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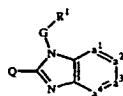
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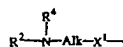
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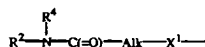
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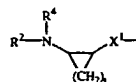
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(b-1)



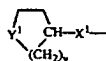
(b-2)



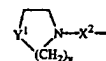
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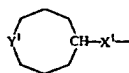
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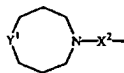
(b-5)



(b-6)



(b-7)



(b-8)

(57) Abstract: This invention concerns the use of compounds of formula (I) wherein -a¹=a²=a³=a⁴- is a radical of formula -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N- wherein each hydrogen atom may optionally be substituted; Q is a radical of formulas (b-1), (b-2), (b-3), (b-4), (b-5), (b-6), (b-7), (b-8), G is a direct bond or C₁₋₁₀alkanediyl; R¹ is an optionally substituted monocyclic heterocycle; for the manufacture of a medicament for the treatment of viral infections, in particular RSV infections. Certain compounds of formula (I) are new.

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RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS

5 The present invention is concerned with benzimidazoles and imidazopyridines having antiviral activity, in particular, they have an inhibitory activity on the replication of the respiratory syncytial virus. It further concerns their preparation and compositions comprising them, as well as their use as a medicine.

10 Human RSV or Respiratory Syncytial Virus is a large RNA virus, member of the family of Paramyxoviridae, subfamily pneumovirinae together with bovine RSV virus. Human RSV is responsible for a spectrum of respiratory tract diseases in people of all ages throughout the world. It is the major cause of lower respiratory tract illness during infancy and childhood. Over half of all infants encounter RSV in their first year of life, and almost all within their first two years. The infection in young children can cause
15 lung damage that persists for years and may contribute to chronic lung disease in later life (chronic wheezing, asthma). Older children and adults often suffer from a (bad) common cold upon RSV infection. In old age, susceptibility again increases, and RSV has been implicated in a number of outbreaks of pneumonia in the aged resulting in significant mortality.

20 Infection with a virus from a given subgroup does not protect against a subsequent infection with an RSV isolate from the same subgroup in the following winter season. Re-infection with RSV is thus common, despite the existence of only two subtypes, A and B.

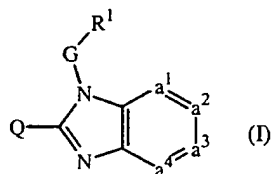
25 Today only three drugs have been approved for use against RSV infection. Ribavirin, a nucleoside analogue, provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly variable efficacy limit its use. The other two
30 drugs, RespiGam[®] and palivizumab, polyclonal and monoclonal antibody immunostimulants, are intended to be used in a preventive way.

Other attempts to develop a safe and effective RSV vaccine have all met with failure thus far. Inactivated vaccines failed to protect against disease, and in fact in some cases
35 enhanced disease during subsequent infection. Live attenuated vaccines have been tried with limited success. Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication.

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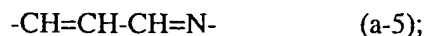
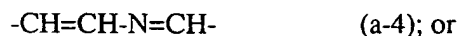
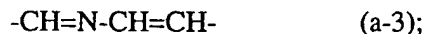
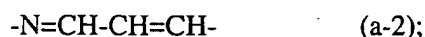
EP-A-0,005,318 , EP-A-0,099,139 , EP-A-0,145,037 , EP-A-0,144,101 ,
 EP-A-0,151,826 , EP-A-0,151,824 , EP-A-0,232,937 , EP-A-0,295,742 , EP 0,297,661 ,
 EP-A-0,307,014 , WO 92 01697 describe benzimidazole and imidazopyridine
 substituted piperidine and piperazine derivatives as antihistaminics, antiallergics or
 5 serotonin antagonists.

The present invention concerns the use of a compound for the manufacture of a
 medicament for treating viral infections, wherein the compound is a compound of
 formula

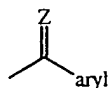


a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex and
 stereochemically isomeric form thereof, wherein

-a¹=a²-a³=a⁴- represents a bivalent radical of formula

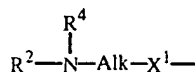


wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may
 optionally be replaced by halo, C₁₋₆alkyl, nitro, amino, hydroxy,
 C₁₋₆alkyloxy, polyhaloC₁₋₆alkyl, carboxyl, aminoC₁₋₆alkyl, mono- or
 di(C₁₋₄alkyl)aminoC₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, hydroxyC₁₋₆alkyl, or a
 radical of formula

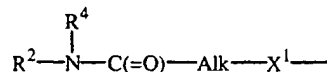


wherein =Z is =O, =CH-C(=O)-NR^{5a}R^{5b}, =CH₂, =CH-C₁₋₆alkyl, =N-OH or
 =N-O-C₁₋₆alkyl;

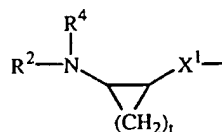
Q is a radical of formula



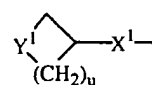
(b-1)



(b-2)

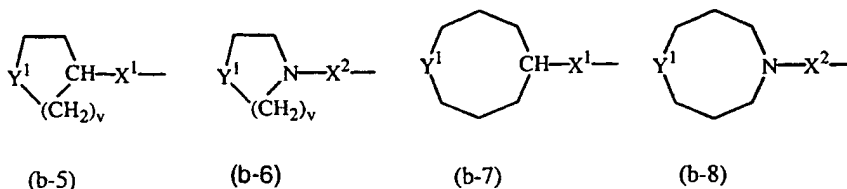


(b-3)



(b-4)

-3-



wherein Alk is C₁₋₆alkanediyl;

Y¹ is a bivalent radical of formula -NR²- or -CH(NR²R⁴)-;

X¹ is NR⁴, S, S(=O), S(=O)₂, O, CH₂, C(=O), C(=CH₂), CH(OH), CH(CH₃),
 5 CH(OCH₃), CH(SCH₃), CH(NR^{5a}R^{5b}), CH₂-NR⁴ or NR⁴-CH₂;

X² is a direct bond, CH₂, C(=O), NR⁴, C₁₋₄alkyl-NR⁴, NR⁴-C₁₋₄alkyl;

t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

- 10 whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R³; with the proviso that when R³ is hydroxy or C₁₋₆alkyloxy, then R³ can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C₁₋₁₀alkanediyl;

- 15 R¹ is a monocyclic heterocycle selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, and isothiazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl,
 20 C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxy carbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-;

each n independently is 1, 2, 3 or 4;

R² is hydrogen, formyl, C₁₋₆alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C₃₋₇cycloalkyl substituted with N(R⁶)₂, or C₁₋₁₀alkyl substituted with N(R⁶)₂ and optionally with a second, third or fourth substituent selected from
 30 amino, hydroxy, C₃₋₇cycloalkyl, C₂₋₅alkanediyl, piperidinyl, mono-or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxy carbonylamino, aryl and aryloxy;

R³ is hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, arylC₁₋₆alkyl or arylC₁₋₆alkyloxy;

R⁴ is hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl;

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R^{5a} , R^{5b} , R^{5c} and R^{5d} each independently are hydrogen or C_{1-6} alkyl; or
 R^{5a} and R^{5b} , or R^{5c} and R^{5d} taken together form a bivalent radical of formula $-(CH_2)_s-$
 wherein s is 4 or 5;

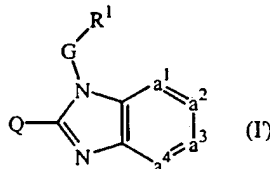
R^6 is hydrogen, C_{1-4} alkyl, formyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyl or
 C_{1-6} alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents
 selected from halo, hydroxy, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, polyhalo C_{1-6} alkyl,
 C_{1-6} alkyloxy; and

Het is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl.

The present invention also relates to a method of treating warm-blooded animals
 suffering from or susceptible to viral infections, in particular RSV infection. Said
 method comprises the administration of a therapeutically effective amount of a
 compound of formula (I) or a prodrug thereof, a *N*-oxide form, a pharmaceutically
 acceptable acid or base addition salt, a quaternary amine, a metal complex or a
 stereochemically isomeric form thereof in admixture with a pharmaceutical carrier.

A further embodiment of the present invention includes the compounds of formula (I')



their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and
 stereochemically isomeric forms, wherein
 $-a^1=a^2-a^3=a^4-$ represents a radical of formula

$-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ (a-1);

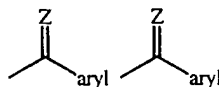
$-\text{N}=\text{CH}-\text{CH}=\text{CH}-$ (a-2);

$-\text{CH}=\text{N}-\text{CH}=\text{CH}-$ (a-3);

$-\text{CH}=\text{CH}-\text{N}=\text{CH}-$ (a-4); or

$-\text{CH}=\text{CH}-\text{CH}=\text{N}-$ (a-5);

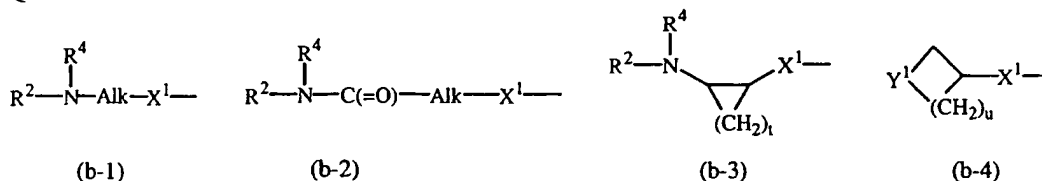
wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may
 optionally be replaced by halo, C_{1-6} alkyl, nitro, amino, hydroxy,
 C_{1-6} alkyloxy, polyhalo C_{1-6} alkyl, carboxyl, amino C_{1-6} alkyl, mono- or
 di(C_{1-4} alkyl)amino C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl, hydroxy C_{1-6} alkyl, or a
 radical of formula



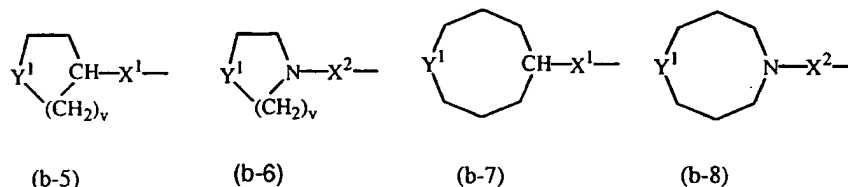
-5-

wherein $=Z$ is $=O$, $=CH-C(=O)-NR^{5a}R^{5b}$, $=CH_2$, $=CH-C_{1-6}alkyl$, $=N-OH$ or $=N-O-C_{1-6}alkyl$;

Q is a radical of formula



5



wherein Alk is $C_{1-6}alkanediyl$;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4 , S, $S(=O)$, $S(=O)_2$, O, CH_2 , $C(=O)$, $C(=CH_2)$, $CH(OH)$, $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2 ;

10

X^2 is a direct bond, CH_2 , $C(=O)$, NR^4 , $C_{1-4}alkyl-NR^4$, $NR^4-C_{1-4}alkyl$;

t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

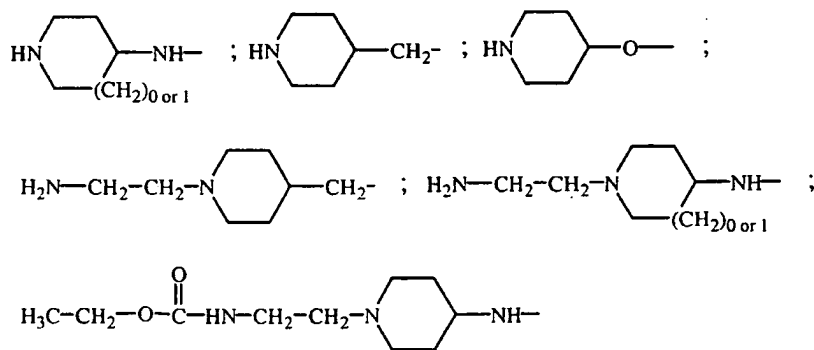
- 15 whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R^3 ; with the proviso that when R^3 is hydroxy or $C_{1-6}alkyloxy$, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or $C_{1-10}alkanediyl$;

- 20 R^1 is a monocyclic heterocycle selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, imidazolyl and pyrazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, $C_{1-6}alkyl$, $C_{1-6}alkyloxy$, $C_{1-6}alkylthio$, $C_{1-6}alkyloxyC_{1-6}alkyl$, aryl, aryl $C_{1-6}alkyl$, aryl $C_{1-6}alkyloxy$, hydroxy $C_{1-6}alkyl$, mono-or
- 25 di($C_{1-6}alkyl$)amino, mono-or di($C_{1-6}alkyl$)amino $C_{1-6}alkyl$, polyhalo $C_{1-6}alkyl$, $C_{1-6}alkyl$ -carbonylamino, $C_{1-6}alkyl-SO_2-NR^{5c}$, aryl- SO_2-NR^{5c} , $C_{1-6}alkyloxycarbonyl$, $-C(=O)-NR^{5c}R^{5d}$, $HO(-CH_2-CH_2-O)_n$, halo $(-CH_2-CH_2-O)_n$, $C_{1-6}alkyloxy(-CH_2-CH_2-O)_n$, aryl $C_{1-6}alkyloxy(-CH_2-CH_2-O)_n$ and mono-or di($C_{1-6}alkyl$)amino $(-CH_2-CH_2-O)_n$;
- each n independently is 1, 2, 3 or 4;

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- R^2 is hydrogen, formyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7} cycloalkyl substituted with $N(R^6)_2$, or C_{1-10} alkyl substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7} cycloalkyl, C_2 -alkanediyl, piperidinyl, mono- or di(C_{1-6} alkyl)amino, C_{1-6} alkyloxycarbonylamino, aryl and aryloxy;
- R^3 is hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy, aryl C_{1-6} alkyl or aryl C_{1-6} alkyloxy;
- R^4 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;
- R^{5a} , R^{5b} , R^{5c} and R^{5d} each independently are hydrogen or C_{1-6} alkyl; or R^{5a} and R^{5b} , or R^{5c} and R^{5d} taken together form a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;
- R^6 is hydrogen, C_{1-4} alkyl, formyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyl or C_{1-6} alkyloxycarbonyl;
- aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, polyhalo C_{1-6} alkyl, and C_{1-6} alkyloxy;
- provided that when G is methylene, and R^1 is 2-pyridyl, 3-pyridyl, 6-methyl-2-pyridyl, 2-pyrazinyl or 5-methyl-imidazol-4-yl, and $-a^1=a^2-a^3=a^4-$ is $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ or $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$, then Q is other than



- Yet another embodiment of the present invention includes the following group of compounds
- 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-5-chloro-7-methyl-1*H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride tetrahydrate;
- N -[1-(2-aminoethyl)-4-piperidinyl]-1-[(2,4-dimethyl-5-oxazolyl)methyl]-1*H*-benzimidazol-2-amine;
- N -[1-(2-aminoethyl)-4-piperidinyl]-1-[(2,5-dimethyl-4-oxazolyl)methyl]-1*H*-benzimidazol-2-amine trihydrochloride monohydrate;
- 4-[[3-[[5-(methoxymethyl)-2-furanyl]methyl]-3*H*-imidazo[4,5-*b*]pyridine-2-yl]methyl]-1-piperidineetanamine;

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- N-[1-(2-aminoethyl)-4-piperidiny]-1-[(5-methyl-3-isoxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate;
- N-[1-(2-aminoethyl)-4-piperidiny]-1-[(2-methyl-5-oxazolyl)methyl]-*1H*-benzimidazol-2-amine monohydrate;
- 5 N-[1-(2-aminoethyl)-4-piperidiny]-1-[(2-methyl-5-oxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate;
- N-[1-(2-aminoethyl)-4-piperidiny]-3-[(2,4-dimethyl-5-oxazolyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine;
- 4-[[3-[(2-methyl-5-oxazolyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]methyl]-1-
- 10 piperazineethanamine;
- N-[1-(2-aminoethyl)-4-piperidiny]-1-(4-thiazolylmethyl)-*1H*-benzimidazol-2-amine;
- N-[1-(2-aminoethyl)-4-piperidiny]-1-[(5-phenyl-1,2,4-oxadiazol-3-yl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride;
- 5-[[2-[[1-(2-aminoethyl)-4-piperidiny]amino]-*1H*-benzimidazol-1-yl]methyl]-2-
- 15 oxazolemethanol tetrahydrochloride dihydrate;
- N-[1-(2-aminoethyl)-4-piperidiny]-1-[(3-methyl-5-isoxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate;
- 4-[[1-[[2-(dimethylamino)-4-thiazolyl]methyl]-*1H*-benzimidazol-2-yl]methyl]-1-
- piperidineethanamine tetrahydrochloride monohydrate 2-propanolate (1:1);
- 20 ethyl 5-[[2-[[1-2-[(1,1-dimethylethoxy)carbonyl]amino]ethyl]-4-piperidiny]amino]-*1H*-benzimidazol-1-yl]methyl]-2-methyl-4-oxazolecarboxylate;
- 4-[[1-[(2-methyl-4-thiazolyl)methyl]-*1H*-benzimidazol-2-yl]methyl]-1-
- piperidineethanamine;
- N-[1-(2-aminoethyl)-4-piperidiny]-1-[(2-methyl-3-furanyl)methyl]-*1H*-benzimidazol-
- 25 2-amine;
- ethyl 4-[[3-[(3-hydroxy-6-methyl-2-pyridiny)methyl]-7-methyl-3H-imidazo[4,5-b]pyridine-2-yl]amino]-1-piperidinecarboxylate;
- 1,1-dimethylethyl 4-[[1-[[3-[2-(dimethylamino)ethoxy]-6-methyl-2-pyridiny]methyl]-*1H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate;
- 30 ethyl 4-[[1-[(3-amino-2-pyridiny)methyl]-*1H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate; and
- N-[1-(6-methyl-2-pyridiny)-*1H*-benzimidazol-2-yl]-1-(3-pyridinylcarbonyl)-4-piperidinamine.
- the prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and
- 35 stereochemically isomeric forms thereof.
- Said group of compounds will be referred to hereinafter as the compounds of group (I').

The term prodrug as used throughout this text means the pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The
5 reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p. 13-15) describing prodrugs generally, is hereby incorporated.

As used herein C₁₋₃alkyl as a group or part of a group defines straight or branched chain
10 saturated hydrocarbon radicals having from 1 to 3 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl and the like; C₁₋₄alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as the group defined for C₁₋₃alkyl and butyl and the like; C₂₋₄alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon
15 radicals having from 2 to 4 carbon atoms such as ethyl, propyl, 1-methylethyl, butyl and the like; C₁₋₆alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C₁₋₄alkyl and pentyl, hexyl, 2-methylbutyl and the like; C₁₋₉alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals
20 having from 1 to 9 carbon atoms such as the groups defined for C₁₋₆alkyl and heptyl, octyl, nonyl, 2-methylhexyl, 2-methylheptyl and the like; C₁₋₁₀alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups defined for C₁₋₉alkyl and decyl, 2-methylnonyl and the like. C₃₋₇cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C₂₋₅alkanediyl defines bivalent straight and branched chain
25 saturated hydrocarbon radicals having from 2 to 5 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,2-propanediyl, 2,3-butanediyl, 1,5-pentanediyl and the like, C₂₋₅alkanediyl is substituted on C₁₋₁₀alkyl as provided for in the definition of R², it is meant to be substituted on one carbon atom thus forming a spiro moiety; C₁₋₄alkanediyl defines bivalent straight and branched chain saturated
30 hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C₁₋₆alkanediyl is meant to include C₁₋₄alkanediyl and the higher homologues thereof having from 5 to 6 carbon atoms such as, for example, 1,5-pentanediyl, 1,6-hexanediyl and the like;
35 C₁₋₁₀alkanediyl is meant to include C₁₋₆alkanediyl and the higher homologues thereof having from 7 to 10 carbon atoms such as, for example, 1,7-heptanediyl, 1,8-octanediyl, 1,9-nonanediyl, 1,10-decanediyl and the like.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom. The term (=N-OH) forms a hydroxylimine moiety when attached to a carbon atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhaloC₁₋₆alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C₁₋₆alkyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhaloC₁₋₆alkyl, they may be the same or different.

When any variable (e.g. aryl, R², R³, R⁴, R^{5a}, R^{5b} etc.) occurs more than one time in any constituent, each definition is independent.

It will be appreciated that some of the compounds of formula (I), (I') or the compounds of group (I'') and their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I), (I') or the compounds of group (I''), and their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I), (I') or the compounds of group (I'') and their prodrugs, *N*-oxides, salts, solvates, quaternary amines, metal complexes substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other isomers. Stereochemically isomeric forms of the compounds of formula (I), (I') or the compounds of group (I'') are obviously intended to be embraced within the scope of this invention.

As used hereinafter the terms trans, cis, R or S are well-known by the person skilled in the art.

For some of the compounds of formula (I), (I') or the compounds of group (I''), their prodrugs, *N*-oxides, salts, solvates, quaternary amines or metal complexes and the intermediates used in the preparation thereof, the absolute stereochemical configuration was not experimentally determined. In these cases the stereoisomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" stereoisomeric forms can be unambiguously characterized by for instance their optical rotation in case "A" and "B" have an enantiomeric relationship. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction. In case "A" and "B" are stereoisomeric mixtures, they can be further separated whereby the respective first fractions isolated are designated "A1" and "B1" and the second as "A2" and "B2", without further reference to the actual stereochemical configuration.

For therapeutic use, salts of the compounds of formula (I), (I') or the compounds of group (I'') are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I), (I') or the compounds of group (I'') are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid), tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I), (I') or the compounds of group (I'') containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, 5 e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates which the 10 compounds of formula (I), (I') or the compounds of group (I'') as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium 15 salts which the compounds of formula (I), (I') or the compounds of group (I'') are able to form by reaction between a basic nitrogen of a compound of formula (I), (I') or the compounds of group (I'') and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as alkyl 20 trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl *p*-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

25 It will be appreciated that the compounds of formula (I), (I') or the compounds of group (I'') may have metal binding, chelating, complexing properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compounds of formula (I), (I') or the compounds of group (I'') are intended to be 30 included within the scope of the present invention.

Some of the compounds of formula (I), (I') or the compounds of group (I'') may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

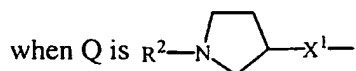
35 A special group of compounds are those compounds of formula (I) or (I') wherein one or more of the following restrictions apply:

- Q is a radical of formula (b-1), (b-3), (b-4), (b-5), (b-6), (b-7) or (b-8);
- X² is a direct bond, CH₂ or C(=O);

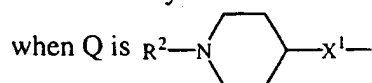
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- R¹ is a monocyclic heterocycle selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, imidazolyl and pyrazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkyl-carbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n;
- 10 - R² is hydrogen, pyrrolidinyl, piperidinyl, homopiperidinyl, C₃₋₇cycloalkyl substituted with NHR⁶, or C₁₋₁₀alkyl substituted with NHR⁶ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C₃₋₇cycloalkyl, C₂₋₅alkanediyl, piperidinyl, mono-or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonylamino, aryl and aryloxy;
- R³ is hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy or arylC₁₋₆alkyl;
- 15 - R⁶ is hydrogen, C₁₋₄alkyl, formyl, C₁₋₆alkylcarbonyl or C₁₋₆alkyloxycarbonyl.

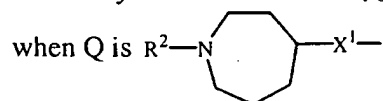
A special group of compounds are those compounds of formula (I') wherein the following restrictions apply :



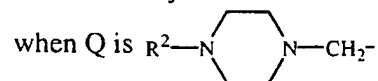
- 20 wherein X¹ is NR⁴, O, S, S(=O), S(=O)₂, CH₂, C(=O), C(=CH₂) or CH(CH₃), then R¹ is other than pyridyl, pyridyl substituted with C₁₋₆alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C₁₋₆alkyl;



- 25 wherein X¹ is NR⁴, O, S, S(=O), S(=O)₂, CH₂, C(=O), C(=CH₂) or CH(CH₃), then R¹ is other than pyridyl, pyridyl substituted with C₁₋₆alkyl, pyridyl substituted with 1 or 2 C₁₋₆alkyloxy, pyrazinyl, pyrrolyl, pyrrolyl substituted with C₁₋₆alkyl, imidazolyl and imidazolyl substituted with C₁₋₆alkyl;

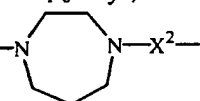


- 30 wherein X¹ is NR⁴, O, S, S(=O), S(=O)₂, CH₂, C(=O), C(=CH₂) or CH(CH₃), then R¹ is other than pyridyl, pyridyl substituted with C₁₋₆alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C₁₋₆alkyl;



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then R¹ is other than pyridyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C₁₋₆alkyl;

when Q is 

wherein X² is CH₂ or a direct bond, then R¹ is other than pyridyl, pyridyl substituted with C₁₋₆alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C₁₋₆alkyl.

Or a special group of compounds are those compounds of formula (I') wherein one of the following applies :

- 10 Q is a radical of formula (b-1); (b-2); (b-3); (b-5); (b-6); (b-7); (b-8); (b-4) wherein u is 1,3,4 or 5; or (b-4) wherein u is 2, wherein Y¹ is -CH(NR²R⁴)-, wherein X¹ is CH(OH), CH(OCH₃), CH(SCH₃), CH(NR^{5a}R^{5b}), CH₂-NR⁴ or NR⁴-CH₂, and wherein R¹ is pyridyl or imidazolyl, each of said heterocycles substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl-
- 15 oxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or
- 20 di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-, or each of said heterocycles substituted with, where possible 2, 3 or 4 C₁₋₆alkyl groups; or wherein R¹ is pyrimidinyl or pyrazinyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy,
- 25 hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or
- 30 di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-, or wherein R¹ is pyrrolyl or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy,
- hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-,
- 35 C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-,

C_{1-6} alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-; or

Q is a radical of formula (b-1); (b-2); (b-3); (b-4); (b-6); (b-7); (b-8); (b-5) wherein v is 3; or (b-5) wherein v is 2, wherein Y¹ is -CH(NR²R⁴)-, wherein X¹ is CH(OH), CH(OCH₃), CH(SCH₃), CH(NR^{5a}R^{5b}), CH₂-NR⁴ or NR⁴-CH₂, and wherein R¹ is pyrrolyl or imidazolyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-, or each of said heterocycles being substituted with, where possible 2, 3 or 4 C₁₋₆alkyl groups; or wherein R¹ is pyridyl being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-, or pyridyl being substituted with, 2, 3 or 4 C₁₋₆alkyl groups or 3 or 4 C₁₋₆alkyloxy groups; or wherein R¹ is pyrazinyl being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-, or where R¹ is pyridazinyl, pyrimidinyl or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-

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O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-;
or

Q is a radical of formula (b-1); (b-2); (b-3); (b-4); (b-6); (b-7); (b-8); (b-5) wherein v is
2; or (b-5) wherein v is 3, wherein Y¹ is -CH(NR²R⁴)-, wherein X¹ is CH(OH),
CH(OCH₃), CH(SCH₃), CH(NR^{5a}R^{5b}), CH₂-NR⁴ or NR⁴-CH₂, and wherein R¹ is pyridyl
or imidazolyl, each of said heterocycles being substituted with 1 or where possible
more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano,
carboxy, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆
alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆
alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-,
aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxy carbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-
CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and
mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-, or each of said heterocycles being
substituted with, where possible 2, 3 or 4 C₁₋₆alkyl groups; or wherein R¹ is pyrimidinyl
or pyrazinyl, each of said heterocycles being substituted with 1 or where possible more,
such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy,
C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆
alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆
alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-,
aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxy carbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-
CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and
mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-, or wherein R¹ is pyrrolyl or pyrazolyl,
each of said heterocycles optionally being substituted with 1 or where possible more,
such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy,
C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆
alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆
alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-,
aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxy carbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-
CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and
mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-, or

Q is a radical of formula (b-1); (b-2); (b-3); (b-4); (b-5); (b-7); (b-8); (b-6) wherein v is
3; or (b-6) wherein v is 2, wherein Y¹ is -CH(NR²R⁴)-, wherein X² is a direct bond or
C(=O), or X² is a direct bond, C(=O), NR⁴, C₁₋₄alkyl-NR⁴, NR⁴-C₁₋₄alkyl, wherein R¹ is
pyridyl, pyrimidinyl or pyrazinyl, each of said heterocycles being substituted with 1 or
where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino,

cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-,

5 halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-; or wherein R¹ is imidazolyl being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or

10 di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-, or imidazolyl being substituted with 2 or 3 C₁₋₆alkyl groups; or wherein R¹ is pyridazinyl,

15 pyrrolyl, or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-,

20 NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-; or

Q is a radical of formula (b-1); (b-2); (b-3); (b-4); (b-5); (b-7); (b-8); (b-6) wherein v is 2; or (b-6) wherein v is 3, Y¹ is -CH(NR²R⁴)-, wherein X² is C(=O) or X² is C(=O), NR⁴, C₁₋₄alkyl-NR⁴, NR⁴-C₁₋₄alkyl, and wherein R¹ is pyridyl or imidazolyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl,

30 mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-, or each of said heterocycles being substituted with, where possible 2, 3 or 4 C₁₋₆alkyl

35 groups; or wherein R¹ is pyrimidinyl or pyrazinyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio,

- C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkyl-carbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-,
- 5 arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-; or wherein R¹ is pyrrolyl or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio,
- C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or
- 10 di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkyl-carbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-.
- 15 Preferred compounds are
- (±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-7-methyl-1*H*-benzimidazol-1-yl)methyl]-6-methyl-3-pyridinol tetrahydrochloride monohydrate;
- 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-1*H*-benzimidazol-1-yl)methyl]-3-pyridinol;
- 20 (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(1,4-dimethyl-1*H*-imidazol-5-yl)methyl]-1*H*-benzimidazol-2-amine monohydrate;
- (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine;
- (±)-2-[[2-[(3-amino-2-hydroxypropyl)amino]-1*H*-benzimidazol-1-yl)methyl]-6-methyl-
- 25 3-pyridinol;
- N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[[3-(2-ethoxyethoxy)-6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine tetrahydrochloride dihydrate;
- (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-chloro-1,4-dimethyl-1*H*-imidazol-5-yl)methyl]-1*H*-benzimidazol-2-amine;
- 30 (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(2-chloro-1,4-dimethyl-1*H*-imidazol-5-yl)methyl]-1*H*-benzimidazol-2-amine;
- (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-methyl-1-[(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine;
- (±)-*N*-[1-(2-aminopropyl)-4-piperidinyl]-1-[(3,5,6-trimethylpyrazinyl)methyl]-1*H*-
- 35 benzimidazol-2-amine tetrahydrochloride trihydrate;
- (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(3,5,6-trimethylpyrazinyl)methyl]-1*H*-benzimidazol-2-amine;

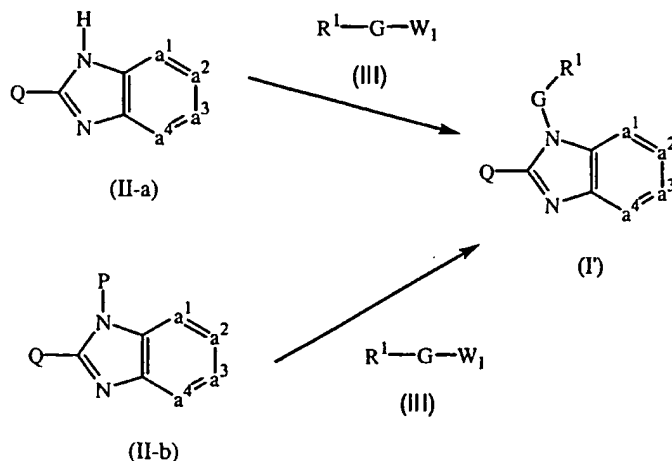
- N-[1-(2-aminoethyl)-4-piperidinyl]-1-[[3-(2-chloroethoxy)-6-methyl-2-pyridinyl]methyl]-*1H*-benzimidazol-2-amine trihydrochloride dihydrate;
 (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[3-amino-2-pyridinyl]methyl]-*1H*-benzimidazol-2-amine tetrahydrochloride trihydrate;
- 5 the prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms thereof.

Most preferred are

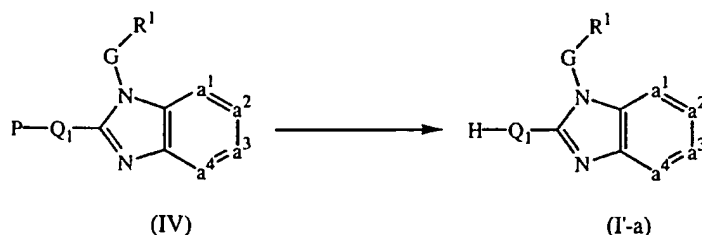
- 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride;
- 10 (±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-7-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl]methyl]-6-methyl-3-pyridinol;
- 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-6-chloro-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride 2-propanolate (1:1);
- 15 (±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol;
- (±)-2-[[2-[[1-(2-aminopropyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride trihydrate;
- 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-7-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride dihydrate;
- 20 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-6-bromo-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride;
- 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride monohydrate;
- 25 (±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol; and
- (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-[(6-methyl-2-pyridinyl)-methyl]-*1H*-benzimidazol-2-amine.
- the prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and
- 30 stereochemically isomeric forms thereof.

- In general, compounds of formula (I') can be prepared by reacting an intermediate of formula (II-a) or (II-b), wherein P represents a protecting group, such as, for example C₁₋₄alkyloxycarbonyl, or those protecting groups mentioned in Chapter 7 of 'Protective
- 35 Groups in Organic Synthesis' by T Greene and P. Wuyts (John Wiley & Sons Inc., 1991), with an intermediate of formula (III), wherein W₁ is a suitable leaving group, such as a halo atom, e.g. chloro, bromo, in the presence of a suitable base, such as, e.g.

sodium hydride, disodium carbonate. Said reaction can be performed in a reaction-inert solvent, such as *N,N*-dimethylformamide.



Compounds of formula (I') wherein, in the definition of Q, R² or at least one R⁶ substituent is hydrogen, said Q being represented by H-Q₁, and said compounds being represented by formula (I'-a), can be prepared by deprotecting an intermediate of formula (IV) wherein P represents a protecting group, for example C₁-alkyloxycarbonyl, benzyl, or those protecting groups mentioned in Chapter 7 of 'Protective Groups in Organic Synthesis' by T Greene and P. Wuyts (John Wiley & Sons Inc., 1991).



When P represents, for example, C₁₋₄alkyloxycarbonyl, said deprotection reaction can be performed by, for example, acidic hydrolysis in the presence of a suitable acid, such as hydrobromic, hydrochloric, sulfuric, acetic, or trifluoroacetic acid or a mixture of said acids, or by alkaline hydrolysis in the presence of a suitable base, such as, for example potassium hydroxide, in a suitable solvent such as water, alcohol, a mixture of water-alcohol, methylene chloride. Suitable alcohols are methanol, ethanol, 2-propanol, 1-butanol and the like. In order to enhance the rate of the reaction, it is advantageous to heat the reaction mixture, in particular up to the reflux temperature.

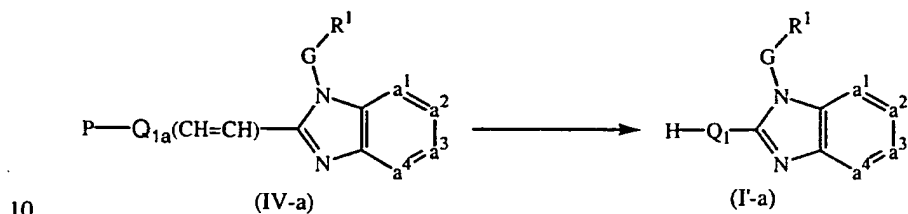
Alternatively, when P represents, for example, benzyl, the deprotection reaction can be performed by catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction-inert solvent. A suitable catalyst in the above reaction is, for

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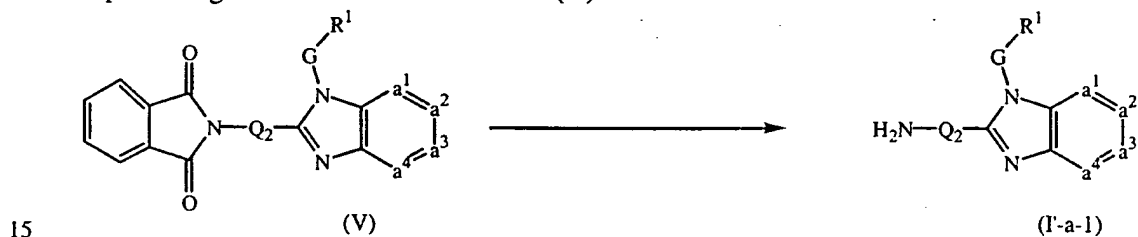
example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g. acetic acid and the like.

5

The catalytic hydrogenation reaction described above can also be used to prepare a compound of formula (I'-a) by deprotecting and reducing an intermediate of formula (IV) wherein Q_1 comprises an unsaturated bond, said Q_1 being represented by $Q_{1a}(CH=CH)$, and said intermediate being represented by formula (IV-a).

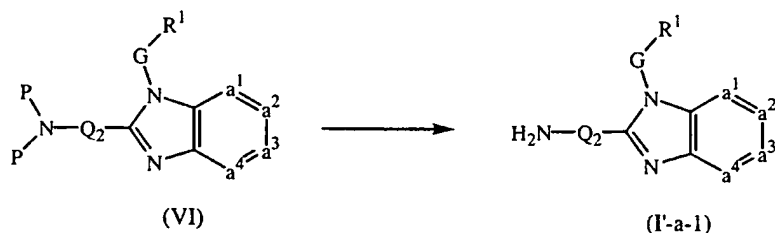


Compounds of formula (I') wherein, in the definition of Q, both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, said Q being represented by H_2N-Q_2 , and said compounds being represented by formula (I'-a-1), can also be prepared by deprotecting an intermediate of formula (V).

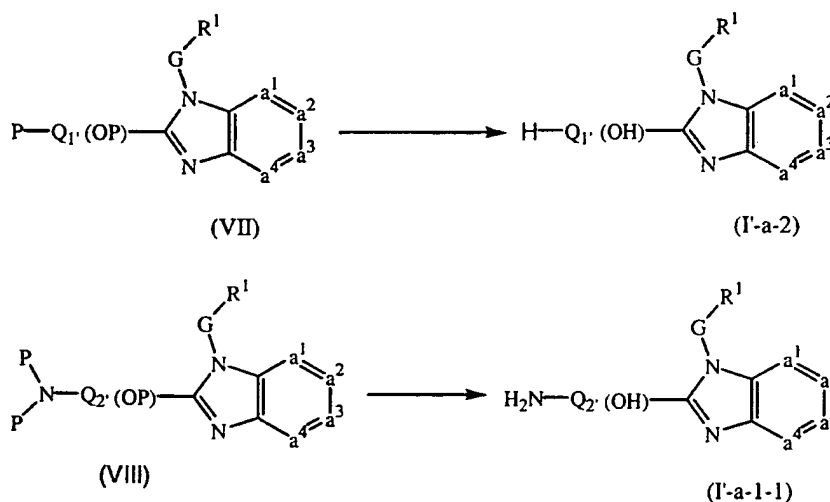


Said deprotection reaction can be performed in the presence of a suitable base such as, for example hydrazine, or in the presence of a suitable acid, such as hydrochloric acid and the like, in a suitable solvent, such as an alcohol, acetic acid and the like.

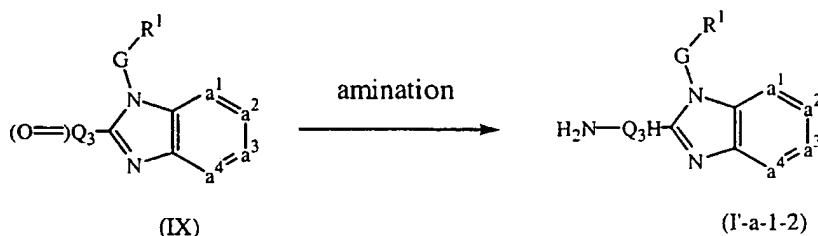
20 Compounds of formula (I'-a-1) can also be prepared by deprotecting an intermediate of formula (VI) according to the procedure described for the preparation of compounds of formula (I'-a).



Compounds of formula (I'-a) or (I'-a-1), wherein Q₁ or Q₂ comprise a hydroxy substituent, said Q₁ or Q₂ being represented by Q₁·(OH) or Q₂·(OH), and said compounds being represented by formula (I'-a-2) or (I'-a-1-1), can be prepared by deprotecting an intermediate of formula (VII) or (VIII) as described hereinabove for the preparation of compounds of formula (I'-a).

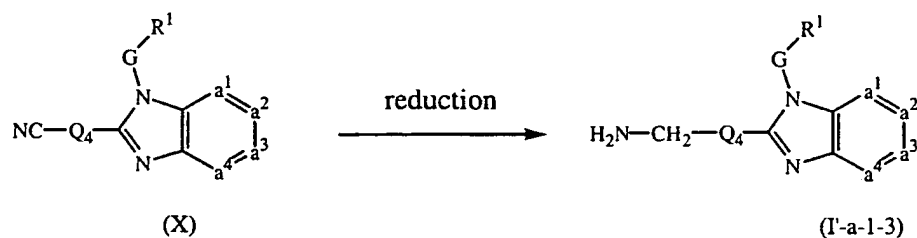


Compounds of formula (I') wherein, in the definition of Q, both R⁶ substituents are hydrogen or R² and R⁴ are both hydrogen, and the carbon adjacent to the nitrogen carrying the R⁶ or R² and R⁴ substituents, contains at least one hydrogen, said Q being represented by H₂N-Q₃H, and said compounds being represented by formula (I'-a-1-2) can also be obtained by reductive amination of intermediates of formula (IX) in the presence of a suitable amination reagent, such as, for example, ammonia, hydroxylamine, or benzylamine, and in the presence of a suitable reducing agent, e.g. hydrogen, and an appropriate catalyst. An appropriate catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, rhodium-on-Al₂O₃, and the like, optionally in the presence of a catalyst poison, such as a thiophene solution. A suitable reaction-inert solvent for the above reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like.

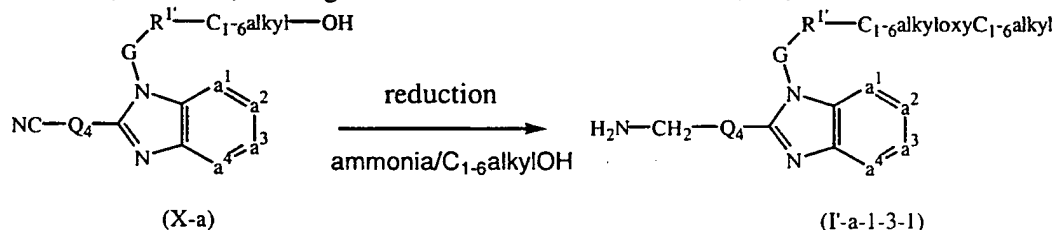


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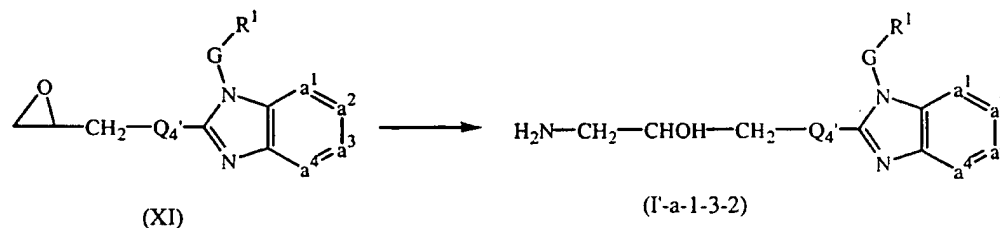
Compounds of formula (I'), wherein Q comprises a $-\text{CH}_2\text{NH}_2$ moiety, said Q being represented by $\text{H}_2\text{N}-\text{CH}_2-\text{Q}_4$, and said compounds being represented by formula (I'-a-1-3) can be prepared by reducing an intermediate of formula (X).



- 5 Said reduction can be performed with a suitable reducing agent, such as lithium aluminium hydride or hydrogen, optionally in the presence of a suitable catalyst, such as Raney Nickel. A suitable solvent for the above reaction is, for example, tetrahydrofuran, or a solution of ammonia in an alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like. Said reduction reaction performed in a
- 10 solution of ammonia in an alcohol can also be used to prepare compounds of formula (I'-a-1-3), wherein R^1 is substituted with $\text{C}_{1-6}\text{alkyloxyC}_{1-6}\text{alkyl}$, said R^1 being represented by $\text{R}^{1'}-\text{C}_{1-6}\text{alkyloxyC}_{1-6}\text{alkyl}$, and said compounds being represented by formula (I'-a-1-3-1) starting from an intermediate of formula (X-a).



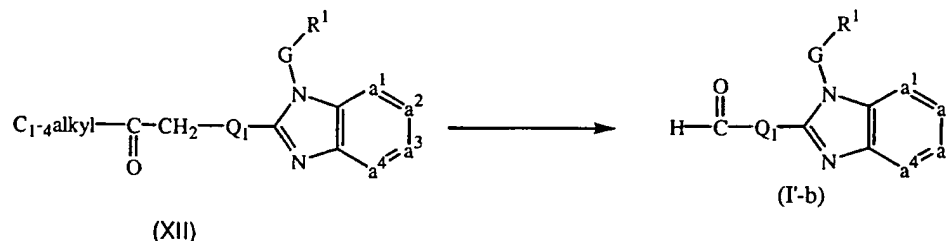
- 15 Compounds of formula (I'), wherein Q comprises a $-\text{CH}_2-\text{CHOH}-\text{CH}_2-\text{NH}_2$ moiety, said Q being represented by $\text{H}_2\text{N}-\text{CH}_2-\text{CHOH}-\text{CH}_2-\text{Q}_4$, and said compounds being represented by formula (I'-a-1-3-2), can be prepared by reacting an intermediate of formula (XI) with ammonia in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. methanol.



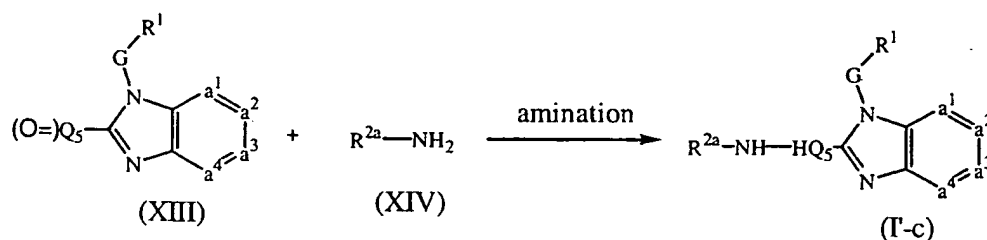
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Compounds of formula (I'), wherein, in the definition of Q, R^2 or one R^6 substituent is formyl, said Q being represented by $\text{H}-\text{C}(=\text{O})-\text{Q}_1$, and said compounds being

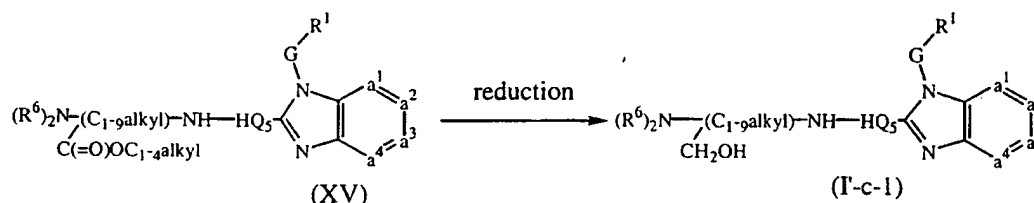
represented by formula (I'-b), can be prepared by reacting an intermediate of formula (XII) with formic acid, formamide and ammonia.



- Compounds of formula (I'), wherein, in the definition of Q, R² is other than hydrogen, said R² being represented by R^{2a}, R⁴ is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R² and R⁴ substituents, carries also at least one hydrogen atom, said Q being represented by R^{2a}-NH-HQ₅, and said compounds being represented by formula (I'-c), can be prepared by reductive amination of an intermediate of formula (XIII) with an intermediate of formula (XIV) in the presence of a suitable reducing agent, such as hydrogen, and a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal, and the like. A suitable reaction-inert solvent for the above reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like.



- Compounds of formula (I'-c), wherein R^{2a} represents C₁₋₁₀alkyl substituted with N(R⁶)₂ and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, said R^{2a} being represented by [(C₁₋₉alkyl)CH₂OH]-N(R⁶)₂, and said compounds being represented by formula (I'-c-1), can be prepared by reducing an intermediate of formula (XV) in the presence of a suitable reducing agent, such as lithium aluminium hydride, in a suitable reaction-inert solvent, such as tetrahydrofuran.

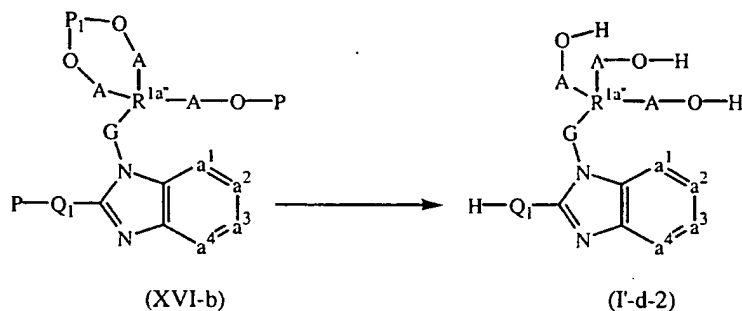
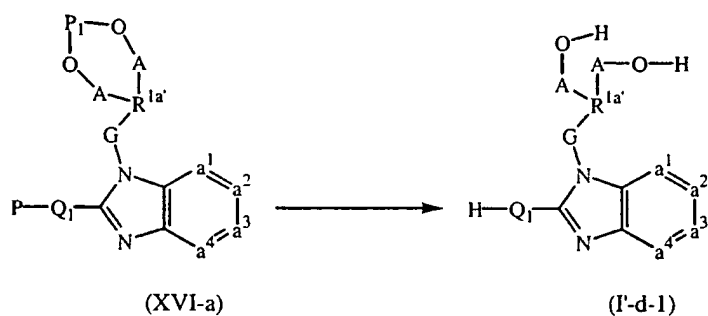
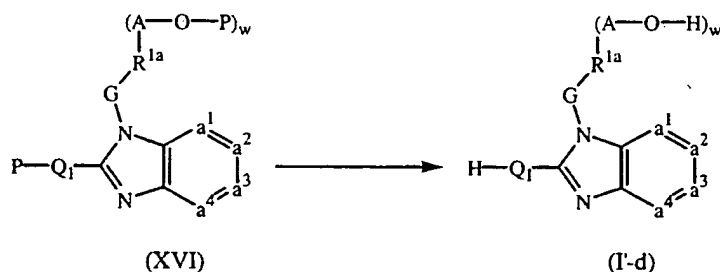


Compounds of formula (I') wherein, in the definition of Q, R² or one R⁶ substituent is hydrogen, said Q being represented by H-Q₁, and wherein R¹ is a monocyclic heterocycle substituted with 1 or more substituents selected from hydroxy,

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hydroxyC₁₋₆alkyl, or HO(-CH₂-CH₂-O)_n-, said substituents being represented by formula A-OH, said R¹ being represented by R^{1a}-(A-OH)_w, with w being the amount of substituents on R^{1a} ranging from 1 to 4, and said compounds being represented by formula (I'-d), can be prepared by deprotecting an intermediate of formula (XVI) with a
 5 suitable acid, such as hydrochloric acid and the like, optionally in the presence of a suitable solvent, such as an alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like.

Alternatively, one protecting group may also protect more than one substituent of R^{1a}, said protecting group being represented by P₁, as represented by formula (XVI-a). The
 10 two ways of protecting the substituents of R^{1a}, i.e. with a separate, as in formula (XVI), or a combined, as in formula (XVI-a), protecting group, may also be combined in the same intermediate, as represented by formula (XVI-b).

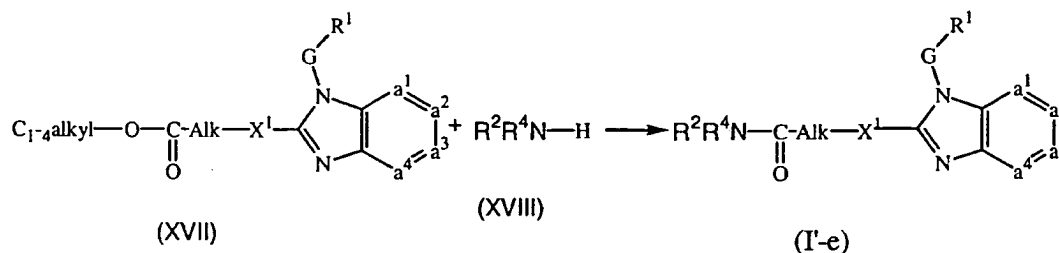


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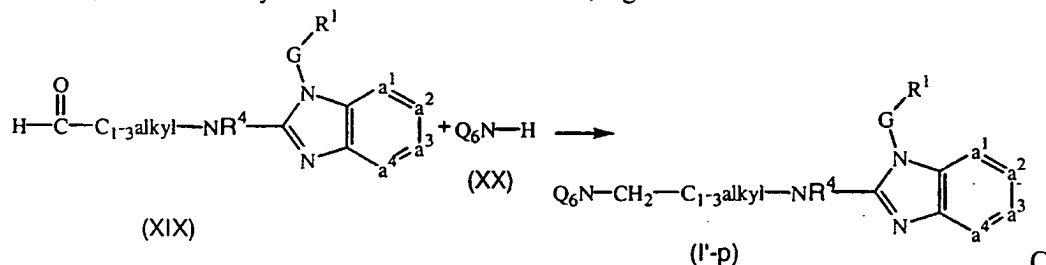
Compounds of formula (I'), wherein Q is a radical of formula (b-2), said compounds being represented by formula (I'-e), can be prepared by reacting an intermediate of formula (XVII) with an intermediate of formula (XVIII) in the presence of sodium

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cyanide and a suitable reaction-inert solvent, such as an alcohol, e.g. methanol and the like.



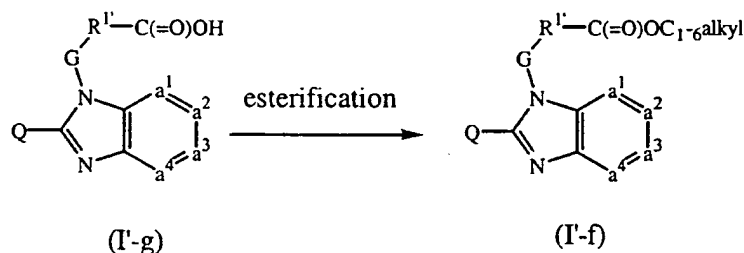
Compounds of formula (I'), wherein in the definition of Q, X² is C₂₋₄alkyl-NR⁴, said Q being represented by Q₆N-CH₂-C₁₋₃alkyl-NR⁴, and said compounds being represented by formula (I'-p), can be prepared by reacting an intermediate of formula (XIX) with an intermediate of formula (XX) in the presence of isopropyl titanate (IV) and a suitable reducing agent, such as NaBH₃CN, and in the presence of a suitable reaction-inert solvent, such as methylene chloride or an alcohol, e.g. ethanol.



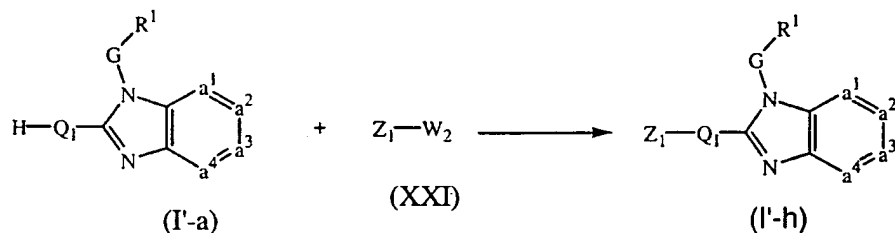
Compounds of formula (I') may be converted into each other following art-known functional group transformation reactions, comprising those described hereinafter.

The compounds of formula (I') may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I') with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboxoperoxoic acid or halo substituted benzenecarboxoperoxoic acid, e.g. 3-chlorobenzenecarboxoperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *t*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

- Compounds of formula (I'), wherein R^1 is monocyclic heterocycle substituted with C_{1-6} alkyloxycarbonyl, said R^1 being represented by $R^{1'}-C(=O)OC_{1-6}alkyl$, and said compounds being represented by formula (I'-f), can be prepared by esterification of a compound of formula (I'-g) in the presence of a suitable alcohol, e.g. methanol, ethanol, propanol, butanol, pentanol, hexanol and the like, and in the presence of a suitable acid, such as hydrochloric acid and the like.

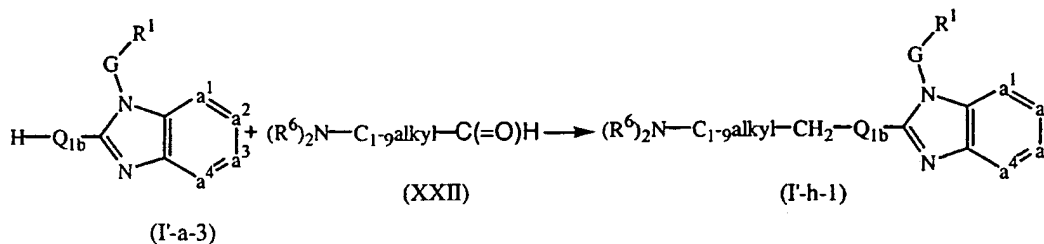


- Compounds of formula (I'-a) may be converted into compounds of formula (I'), wherein, in the definition of Q, R^2 or at least one R^6 substituent is other than hydrogen, said R^2 or R^6 being represented by Z_1 , said Q being represented by Z_1-Q_1 , and said compounds being represented by formula (I'-h), by reaction with a reagent of formula (XXI), wherein W_2 is a suitable leaving group, such as a halo atom, e.g. bromo, or 4-methylbenzenesulphonate, in the presence of a suitable base, such as, for example disodium carbonate, dipotassium carbonate, sodium hydroxide and the like, in a reaction-inert solvent, e.g. 3-methyl-2-butanone, acetonitrile, *N,N*-dimethylformamide.

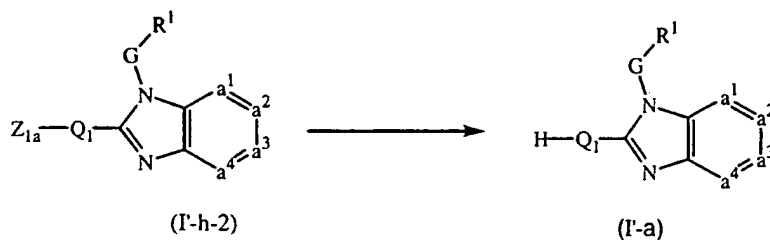


- Compounds of formula (I'-h), wherein, in the definition of Z_1 , R^2 is $CH_2-C_{1-9}alkyl$ substituted with $N(R^6)_2$, said compounds being represented by formula (I'-h-1), can also be prepared by reacting a compound of formula (I'-a) wherein, in the definition of $H-Q_1$, R^2 is hydrogen, said $H-Q_1$ being represented by $H-Q_{1b}$, and said compounds being represented by formula (I'-a-3), with an intermediate of formula (XXII), in the presence of a suitable reducing agent, such as sodium cyanoborohydride, in a suitable reaction-inert solvent, such as an alcohol.

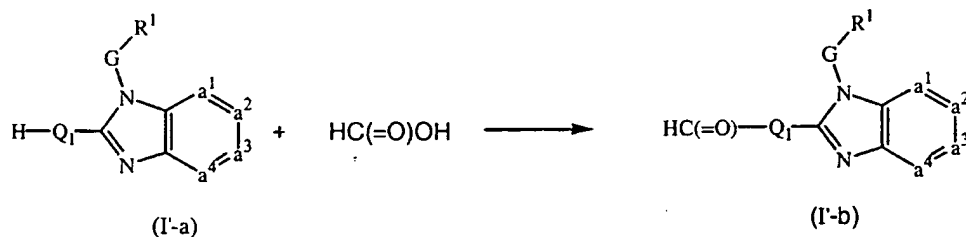
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Compounds of formula (I'-h), wherein Z₁ comprises formyl, C₁₋₆alkylcarbonyl, or C₁₋₆alkyloxycarbonyl, said Z₁ being represented by Z_{1a}, and said compounds being represented by formula (I'-h-2), can be converted into compounds of formula (I'-a), by acidic hydrolysis in the presence of a suitable acid, such as hydrobromic, hydrochloric, sulfuric, acetic, or trifluoroacetic acid or a mixture of said acids, or by alkaline hydrolysis in the presence of a suitable base, such as, for example potassium hydroxide, in a suitable solvent such as water, alcohol, a mixture of water-alcohol, methylene chloride. Suitable alcohols are methanol, ethanol, 2-propanol, 1-butanol, sec. butanol and the like. In order to enhance the rate of the reaction, it is advantageous to work at elevated temperatures.



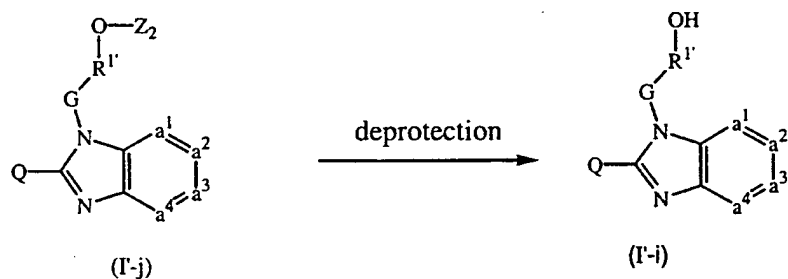
Compounds of formula (I'-b) can be prepared by reacting a compound of formula (I'-a) with formic acid.



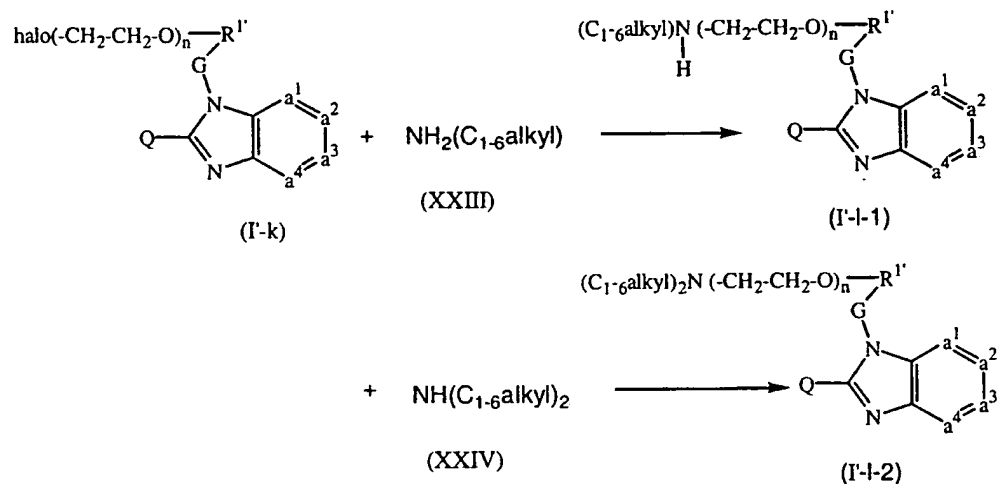
Compounds of formula (I') wherein R¹ is monocyclic heterocycle substituted with hydroxy, said R¹ being represented by HO-R^{1'}, and said compounds being represented by formula (I'-i), can be prepared by deprotecting a compound of formula (I'-j), wherein R¹ is monocyclic heterocycle substituted with C₁₋₆alkyloxy or arylC₁₋₆alkyloxy, said C₁₋₆alkyl or arylC₁₋₆alkyl being represented by Z₂, and said R¹ being represented by Z₂-O-R^{1'}. Said deprotection can be performed in a reaction-inert solvent, such as, for

-28-

example methylene chloride, in the presence of a suitable deprotecting agent, e.g. tribromoborane.

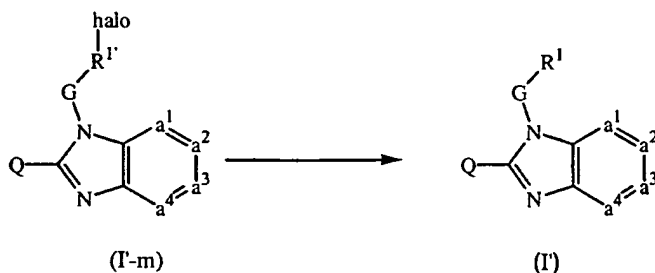


- Compounds of formula (I') wherein R¹ is monocyclic heterocycle substituted with halo(-CH₂-CH₂-O)_n, said compounds being represented by formula (I'-k), can be converted into a compound of formula (I'-l-1) or (I'-l-2) by reaction with the appropriate amine of formula (XXIII) or (XXIV) in a suitable reaction-inert solvent, e.g. tetrahydrofuran.

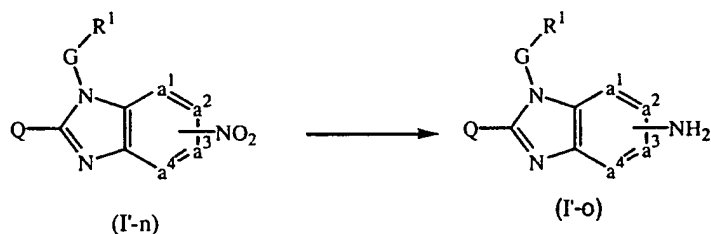


- Compounds of formula (I'), wherein R¹ is monocyclic heterocycle substituted with halo, said compounds being represented by formula (I'-m) can be converted into compounds of formula (I') by reaction with 1-butanethiol in the presence of palladium-on-charcoal and CaO in a suitable reaction-inert solvent, such as tetrahydrofuran.

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- Compounds of formula (I') wherein a hydrogen atom in the radicals of formula (a-1), (a-2), (a-3), (a-4) or (a-5) is replaced by nitro, said compounds being represented by formula (I'-n) may be reduced to a compound of formula (I'-o) in the presence of a suitable reducing agent, such as hydrogen, in the presence of a suitable catalyst, such as platinum-on-charcoal, and optionally in the presence of a suitable catalyst poison, e.g. a thiophene solution. The reaction may be performed in a suitable reaction-inert solvent, such as an alcohol.



- The reactions described hereinabove for the preparation of the compounds of formula (I') can also be used to prepare the compounds of the group (I'').

In the following paragraphs, there are described several methods of preparing the intermediates in the foregoing preparations. A number of intermediates and starting materials are commercially available or are known compounds which may be prepared according to conventional reaction procedures generally known in the art or analogous to the procedures described in EP-A-0,005,318 , EP-A-0,099,139 , EP-A-0,151,824 , EP-A-0,151,826 , EP-A-0,232,937 , EP-A-0,295,742 , EP-A-0,297,661 , EP-A-0,539,420 , EP-A-0,539,421 , US 4,634,704 , US 4,695,569.

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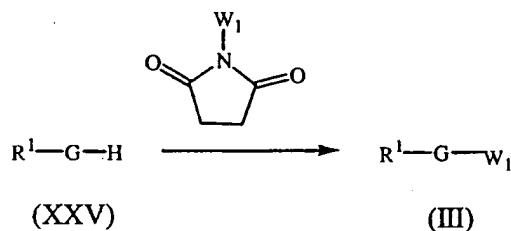
In the foregoing and the following preparations, the reaction mixture is worked up following art-known methods and the reaction product is isolated and, if necessary, further purified.

- Intermediates of formula (III) can be prepared by reacting an intermediate of formula (XXV) with a suitable leaving group, i.e. W₁, introducing agent, e.g. 1-halo-

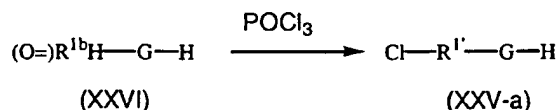
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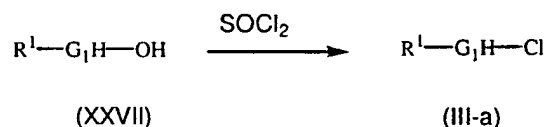
2,5-pyrrolidinedione, in the presence of dibenzoyl peroxide, in a reaction-inert solvent, e.g. tetrachloromethane.



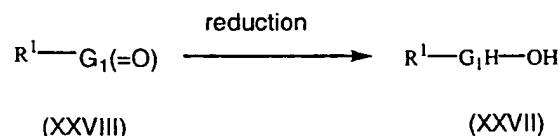
Intermediates of formula (XXV), wherein R¹ is monocyclic heterocycle substituted with chloro, said R¹ being represented by Cl-R^{1'} and said intermediates being represented by formula (XXV-a), can be prepared by reacting an intermediate of formula (XXVI), wherein (O=)R^{1b}H is defined as a carbonyl derivative of R^{1'} wherein one carbon or nitrogen, adjacent to the carbonyl, carries at least one hydrogen, with phosphorus oxychloride. Intermediates of formula (XXVI) may also react as their enol tautomeric forms.



Intermediates of formula (III) wherein W₁ is chloro, which is attached to a carbon atom carrying at least one hydrogen, said G being represented by G₁H, and said intermediates being represented by formula (III-a), can also be prepared by reacting an intermediate of formula (XXVII) with thionylchloride in a reaction-inert solvent, e.g. methylene chloride.



Intermediates of formula (XXVII) can be prepared by reducing an intermediate of formula (XXVIII) in a reaction-inert solvent, e.g. an alcohol, in the presence of a suitable reducing agent, e.g. sodium borohydride.

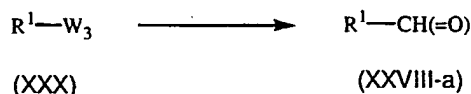


Alternatively, intermediates of formula (XXVII) can also be prepared by deprotecting an intermediate of formula (XXIX), wherein P is a suitable protecting group, e.g. C₁₋₄alkylcarbonyl, in a reaction-inert solvent, such as an alcohol, in the presence of a suitable base, e.g. sodium hydroxide.

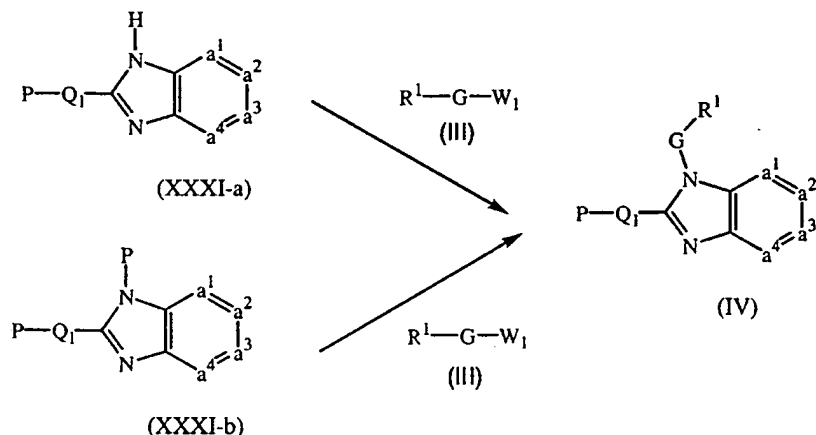
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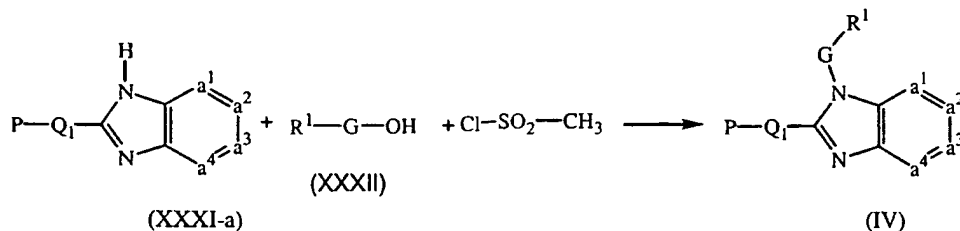
- Intermediates of formula (XXVIII), wherein $\text{G}_1(=\text{O})$ is $\text{CH}(=\text{O})$, said intermediates being represented by formula (XXVIII-a), can be prepared by reacting an intermediate of formula (XXX), wherein W_3 is a suitable leaving group, such as a halo atom, e.g. bromo, with *N,N*-dimethylformamide in the presence of butyllithium in a reaction-inert solvent, e.g. tetrahydrofuran, diethylether or a mixture thereof.



- Intermediates of formula (IV) can be prepared by reacting an intermediate of formula (XXXI-a) or (XXXI-b), wherein P represents a suitable protecting group, such as, for example, C_{1-4} alkyloxycarbonyl, with an intermediate of formula (III) according to the reaction described for the general preparation of compounds of formula (I').

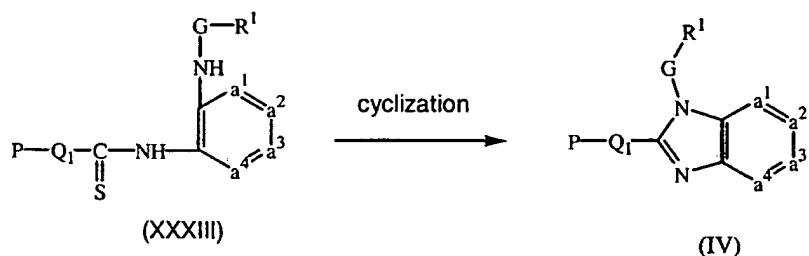


- Intermediates of formula (IV) can also be prepared by reacting an intermediate of formula (XXXI-a) with an intermediate of formula (XXXII) that has reacted with methanesulfonyl chloride, in the presence of a suitable base, such as sodium hydride, and in the presence of a suitable reaction-inert solvent, e.g. *N,N*-dimethylformamide.

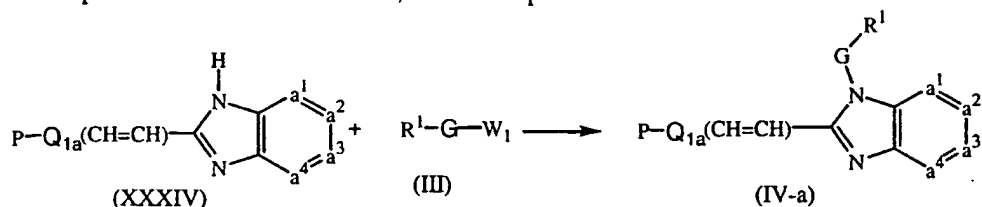


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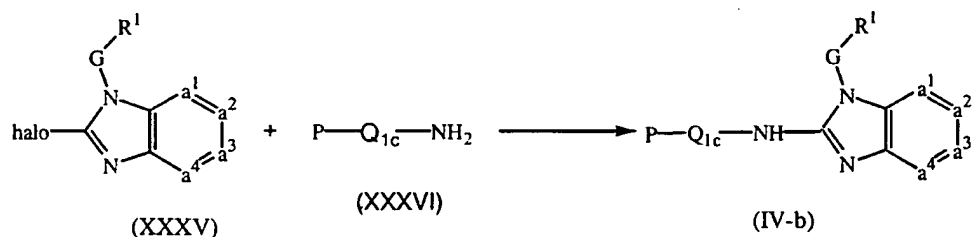
Intermediates of formula (IV) can also be prepared by a cyclization reaction of an intermediate of formula (XXXIII) in a reaction-inert solvent, e.g. an alcohol or *N,N*-dimethylformamide, in the presence of mercury oxide and sulphur.



- 5 Intermediates of formula (IV) wherein Q_1 comprises an unsaturated bond, said Q_1 being represented by $Q_{1a}(\text{CH}=\text{CH})$, and said intermediates by formula (IV-a), can be prepared by reacting an intermediate of formula (XXXIV) with an intermediate of formula (III) in the presence of a suitable base, such as dipotassium carbonate.

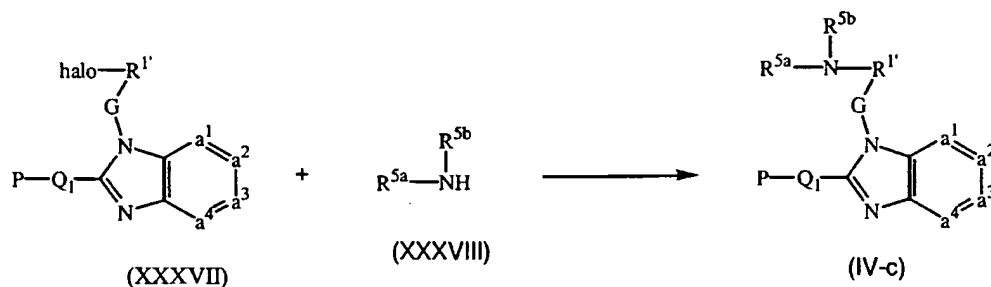


- 10 Intermediates of formula (IV) wherein, in the definition of Q_1 , the X^1 or X^2 moieties in the radicals of formula (b-1) to (b-8) represent NH, said Q_1 being represented by $Q_{1c}\text{-NH}$, and said intermediates by formula (IV-b), may also be prepared by reacting an intermediate of formula (XXXV) with an intermediate of formula (XXXVI).

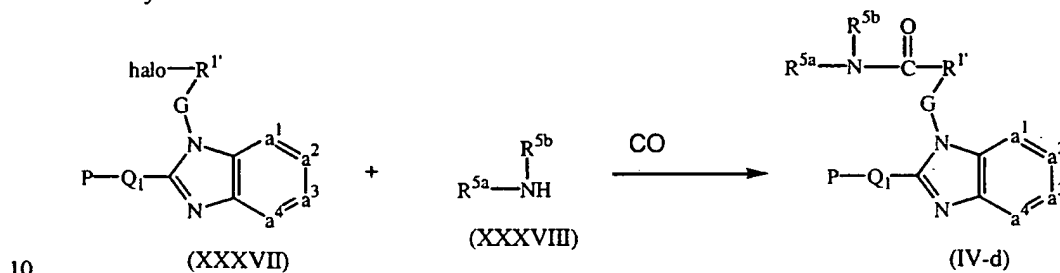


- 15 Intermediates of formula (IV) wherein R^1 is monocyclic heterocycle substituted with amino or mono- or di(C_{1-6} alkyl)amino, said R^1 being represented by $R^{5a}R^{5b}N\text{-}R^{1'}$, wherein R^{5a} and R^{5b} are defined as described hereinabove, and said intermediates being represented by formula (IV-c), can be prepared by reacting an intermediate of formula (XXXVII) with an appropriate amine, represented by formula (XXXVIII), in the presence of an appropriate catalyst, e.g. palladium, and (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.
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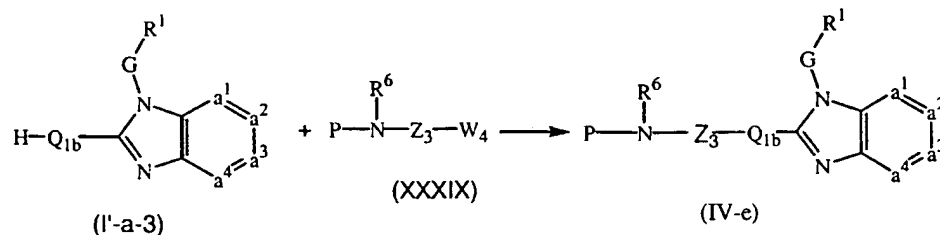
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Intermediates of formula (IV) wherein R^1 is monocyclic heterocycle substituted with $\text{C}(=\text{O})-\text{NR}^{5a}\text{R}^{5b}$, wherein R^{5a} and R^{5b} are defined as described hereinabove, said R^1 being represented by $\text{R}^{5a}\text{R}^{5b}\text{N}-\text{C}(=\text{O})-\text{R}^{1'}$, and said intermediates being represented by
 5 formula (IV-d), can be prepared by reacting an intermediate of formula (XXXVII) with an appropriate amine, represented by formula (XXXVIII), under an atmosphere of carbon monoxide, in the presence of a suitable catalyst, e.g. palladium (II) acetate, and 1,3-bis(diphenylphosphino)propane, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



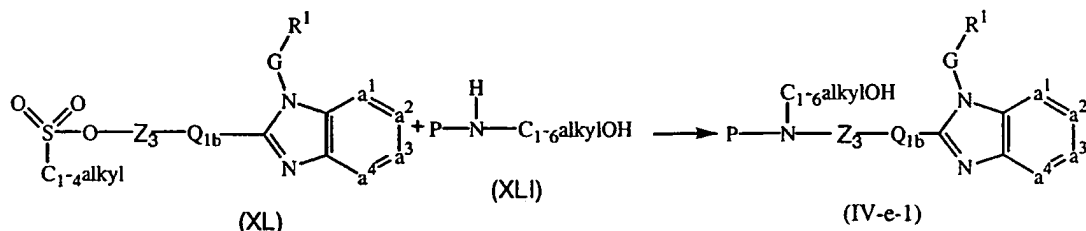
Intermediates of formula (IV) wherein $\text{P}-\text{Q}_1$ comprises C_{1-10} alkyl or C_{3-7} cycloalkyl substituted with NR^6-P , said C_{1-10} alkyl or C_{3-7} cycloalkyl being represented by Z_3 , said $\text{P}-\text{Q}_1$ being represented by $\text{P}-\text{N}^6-\text{Z}_3-\text{Q}_{1b}$, and said intermediates being represented by
 15 formula (IV-e), can be prepared by reacting a compound of formula (I'-a-3) with an intermediate of formula (XXXIX), wherein W_4 represents a suitable leaving group, such as p-toluenesulphonate. Said reaction can be performed in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



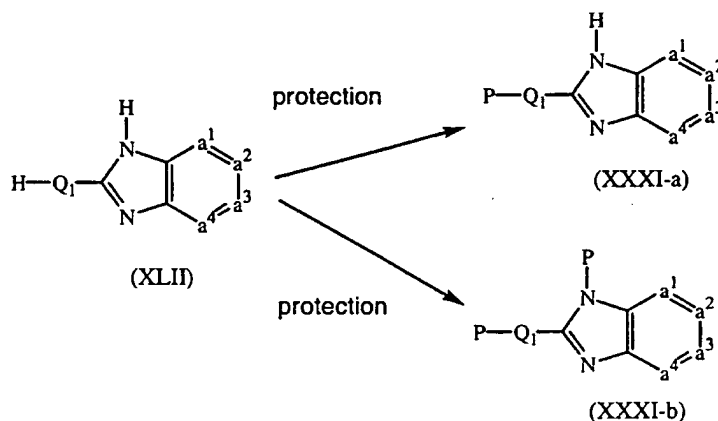
Intermediates of formula (IV-e), wherein R^6 is hydroxy C_{1-6} alkyl, said intermediates
 20 being represented by formula (IV-e-1), can be prepared by reacting an intermediate of

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formula (XL) with an intermediate of formula (XLI) in the presence of a suitable base, e.g. dipotassium carbonate, and a suitable solvent, e.g. acetonitrile.



- Intermediates of formula (XXXI-a) or (XXXI-b) can be prepared by protecting an intermediate of formula (XLII) with a suitable protecting group, such as, for example, $C_{1-4}alkyloxycarbonyl$, in a reaction-inert solvent, such as methylene chloride or an alcohol, e.g. methanol, ethanol, 2-propanol and the like, in the presence of a suitable reagent, e.g. $diC_{1-4}alkyldicarbonate$, and optionally in the presence of a suitable base, e.g. sodium acetate.



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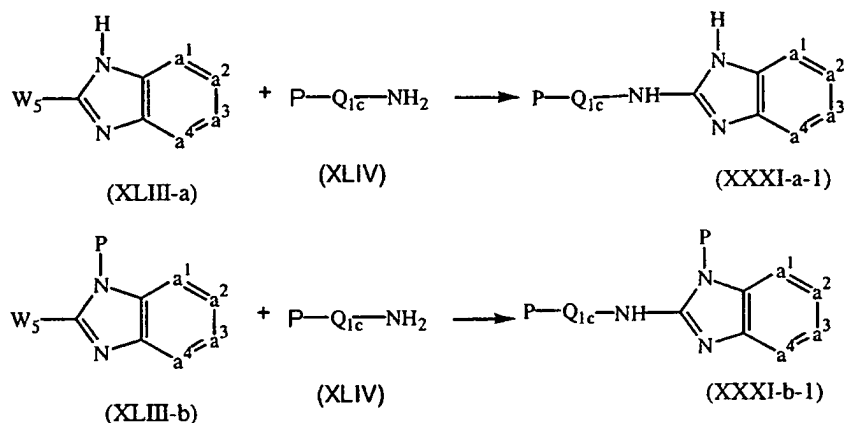
Alternatively, intermediates of formula (XXXI-a) or (XXXI-b) can be converted into an intermediate of formula (XLII) by reaction with a suitable acid, such as hydrochloric acid or hydrobromic acid and the like or mixtures thereof, in the presence of a suitable solvent, e.g. water.

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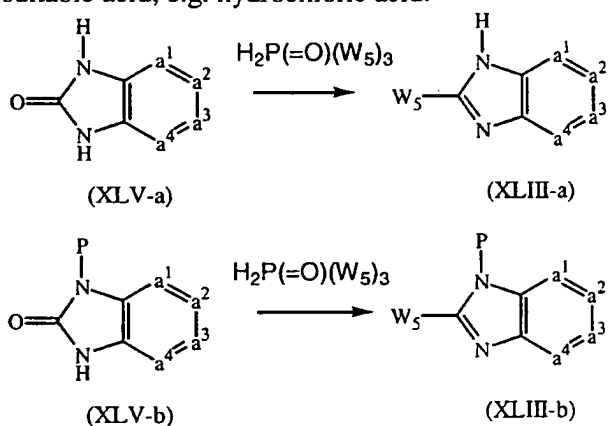
- Intermediates of formula (XXXI-a) or (XXXI-b), wherein in the definition of Q_1 , the X^1 or X^2 moieties in the radicals of formula (b-1) to (b-8) represent NH , said Q_1 being represented by $Q_{1c}-NH$, and said intermediates by formula (XXXI-a-1) or (XXXI-b-1), can be prepared by reacting an intermediate of formula (XLIII-a) or (XLIII-b), wherein W_5 represents a suitable leaving group, such as for example a halo atom, e.g. chloro, with an intermediate of formula (XLIV).

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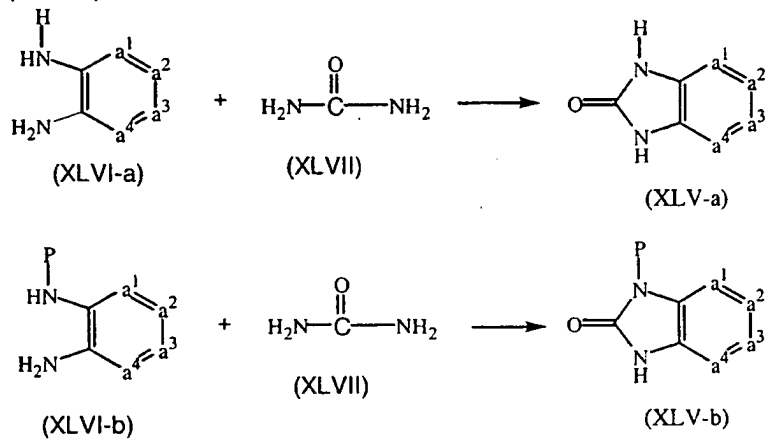


Intermediates of formula (XLIII-a) or (XLIII-b) can be prepared by reacting an intermediate of formula (XLV-a) or (XLV-b) with $\text{H}_2\text{P}(=\text{O})(\text{W}_5)_3$ in the presence of a suitable acid, e.g. hydrochloric acid.

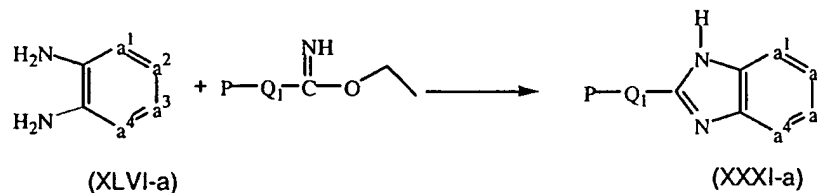


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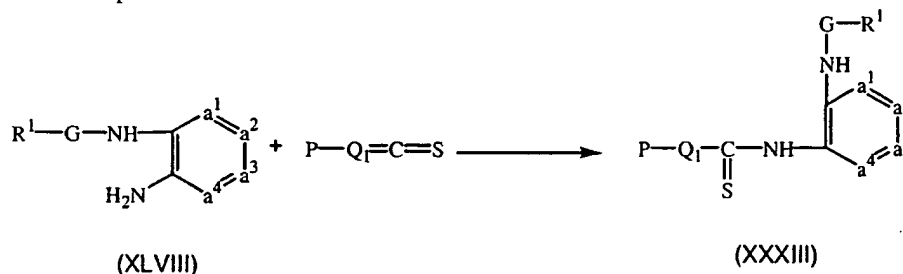
Intermediates of formula (XLV-a) or (XLV-b) can be prepared by reacting an intermediate of formula (XLVI-a) or (XLVI-b) with an intermediate of formula (XLVII).



Intermediates of formula (XXXI-a) can also be prepared by reacting an intermediate of formula (XLVI-a) with $P-Q_1-C(=NH)-O-CH_2-CH_3$ in a reaction-inert solvent, such as an alcohol.

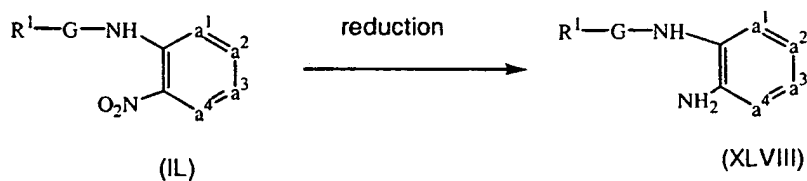


- 5 Intermediates of formula (XXXIII) can be prepared by reacting an intermediate of formula (XLVIII) with an intermediate of formula $P-Q_1-C=S$, which is synthesized according to the procedures described in EP 0005318, in a reaction-inert solvent, such as an alcohol, e.g. ethanol. To increase the reaction rate, the reaction may be performed at elevated temperatures.

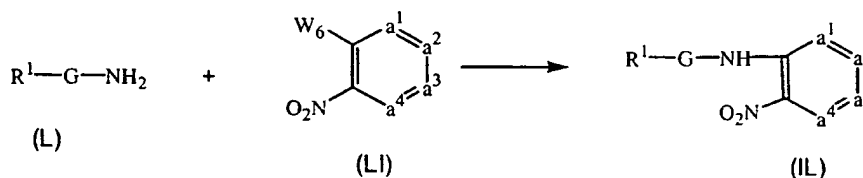


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Intermediates of formula (XLVIII) can be obtained by reducing an intermediate of formula (II) in a reaction-inert solvent, e.g. an alcohol, in the presence of a suitable reducing agent, e.g. hydrogen, and an appropriate catalyst, e.g. Raney Nickel.

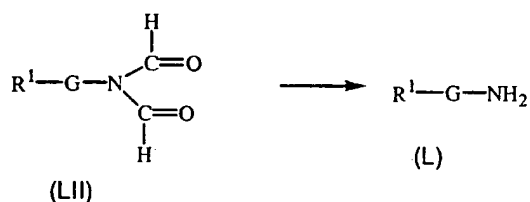


- 15 Intermediates of formula (II) can be prepared by reacting an intermediate of formula (L) with an intermediate of formula (LI), in which W_6 represents a suitable leaving group, such as a halo atom, e.g. chloro. The reaction may be performed in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.

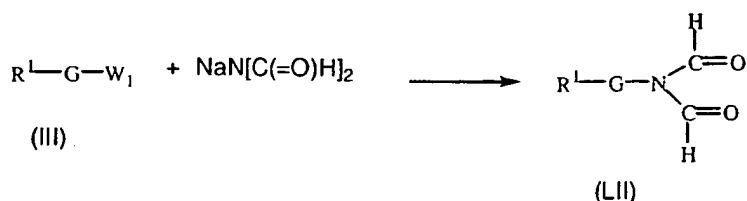


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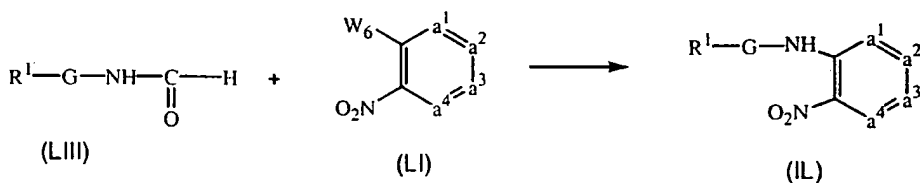
Intermediates of formula (L) can be prepared by reacting an intermediate of formula (LII) with a suitable acid, such as hydrochloric acid, in the presence of a suitable solvent, e.g. an alcohol, e.g. ethanol.



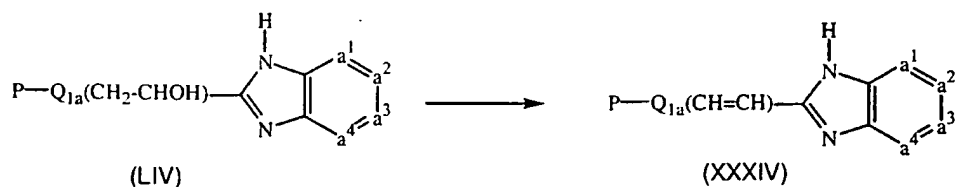
- 5 Intermediates of formula (LII) can be prepared by reacting an intermediate of formula (III) with $\text{NaN}[\text{C}(=\text{O})\text{H}]_2$.



- Intermediates of formula (IL) can also be prepared by reacting an intermediate of formula (LI) with an intermediate of formula (LIII) (J. Org. Chem., 25, p 1138, 1960) in a reaction-inert solvent, e.g. *N,N*-dimethylformamide, in the presence of an appropriate base, e.g. sodium hydride.

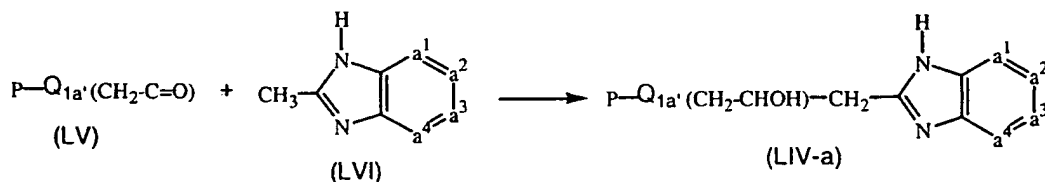


Intermediates of formula (XXXIV) can be prepared by dehydrating an intermediate of formula (LIV) with a suitable acid, such as sulfuric acid.

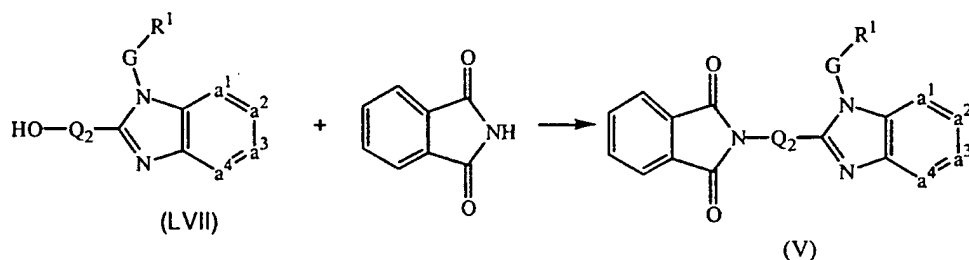


- Intermediates of formula (LIV) wherein, in the definition of Q_{1a} , the X^1 or X^2 moieties are CH_2 , said Q_{1a} being represented by $\text{Q}_{1a'}$, and said intermediates being represented by formula (LIV-a), can be prepared by reacting a carbonyl moiety of formula (LV) with an intermediate of formula (LVI) in the presence of *N,N*-diisopropylamine and butyl lithium, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.

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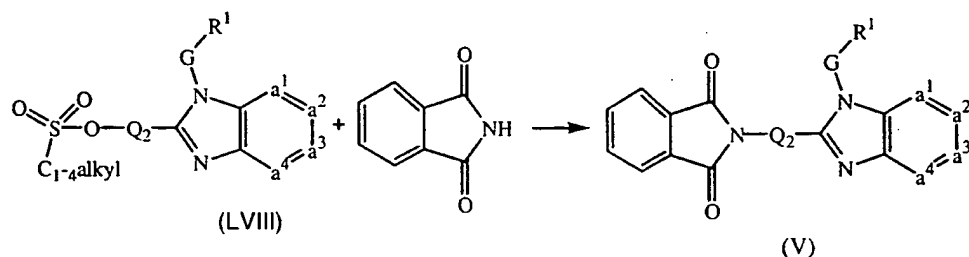


Intermediates of formula (V) can be prepared by reacting an intermediate of formula (LVII) with 1*H*-isoindole-1,3 (2*H*)-dione in the presence of triphenylphosphine and diethyl azodicarboxylate.

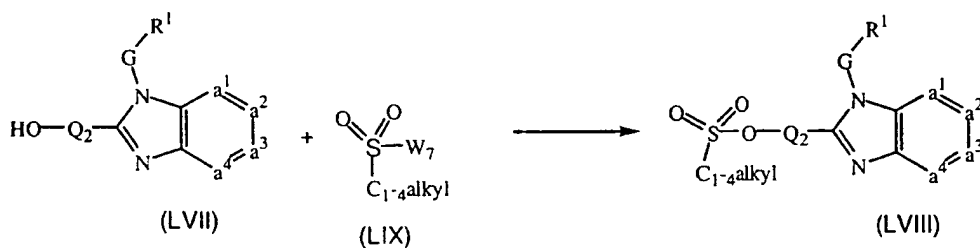


5

Intermediates of formula (V) may also be prepared by reacting an intermediate of formula (LVIII) with 1*H*-isoindole-1,3 (2*H*)-dione in the presence of a suitable base, such as sodium hydride, and a suitable solvent, such as *N,N*-dimethylformamide.

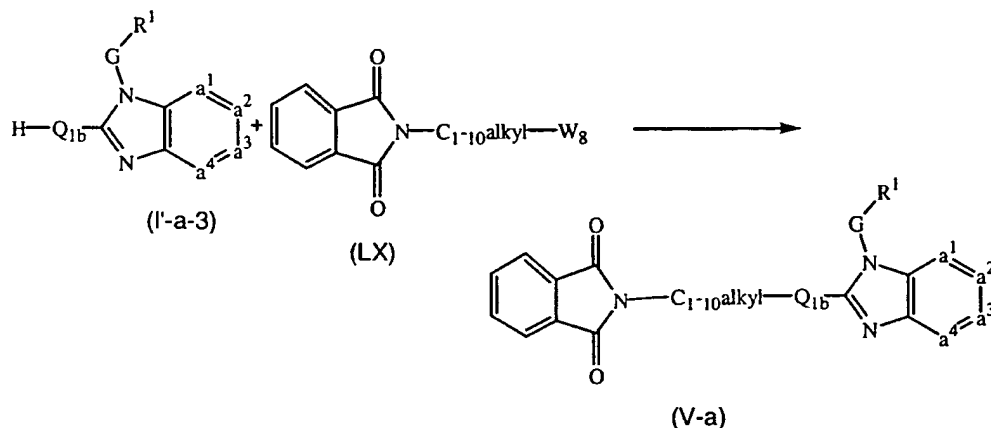


- 10 Intermediates of formula (LVIII) can be prepared by reacting an intermediate of formula (LVII) with an intermediate of formula (LIX), wherein W_7 represents a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as *N,N*-diethyl-ethanamine, and a suitable solvent, such as methylene chloride.

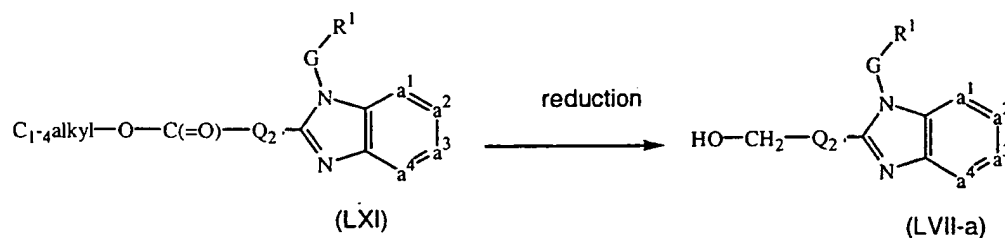


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- Intermediates of formula (V), wherein in the definition of Q_2 , R^2 is C_{1-10} alkyl, said Q_2 being represented by C_{1-10} alkyl- Q_{1b} , and said intermediates by formula (V-a), can be prepared by reacting a compound of formula (I'-a-3) with an intermediate of formula (LX), wherein W_8 is a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as dipotassium carbonate, and a suitable solvent, such as acetonitrile.

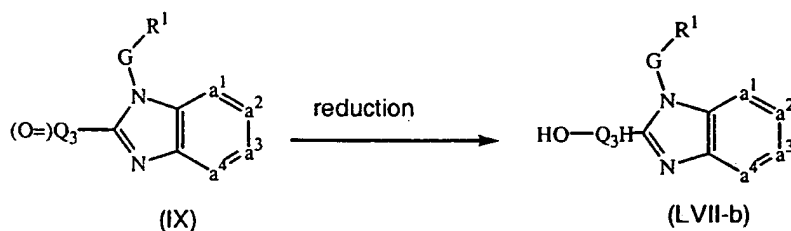


- Intermediates of formula (LVII) wherein, in the definition of Q_2 , the carbon atom carrying the hydroxy, also carries two hydrogen atoms, said $HO-Q_2$ being represented by $HO-CH_2-Q_2$, and said intermediates being represented by formula (LVII-a), can be prepared by reducing an intermediate of formula (LXI) in the presence of a suitable reducing agent, such as lithium aluminium hydride, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.

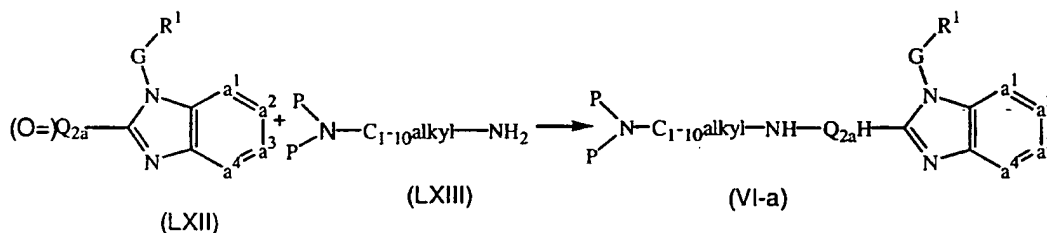


- Intermediates of formula (LVII), wherein, in the definition of Q_2 , the carbon atom carrying the hydroxy, carries also at least one hydrogen, said $HO-Q_2$ being represented by $HO-Q_3H$, and said intermediates being represented by formula (LVII-b), can be prepared by reducing an intermediate of formula (IX) with a suitable reducing agent, e.g. sodium borohydride, in a reaction-inert solvent, e.g. an alcohol.

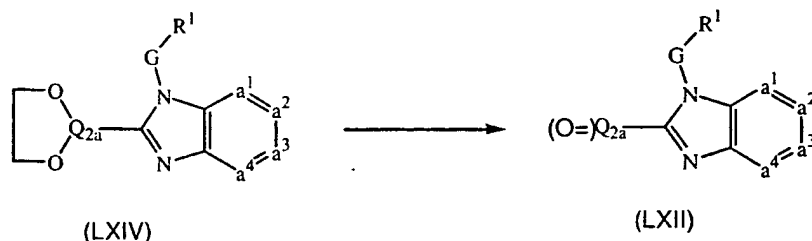
-40-



Intermediates of formula (VI) wherein, in the definition of Q₂, R² is C₁₋₁₀alkyl substituted with N(P)₂ and the carbon atom adjacent to the nitrogen atom carrying the R² substituent carries also at least one hydrogen atom, said Q₂ being represented by
 5 (P)₂-N-C₁₋₁₀alkyl-NH-Q_{2a}H, and said intermediates being represented by formula (VI-a), can be prepared by reductive amination of an intermediate of formula (LXII) with an intermediate of formula (LXIII) in the presence of a suitable reductive agent, such as hydrogen, and a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal, and the like, and optionally in the presence of a suitable catalyst poison, such as a thiophene solution. A suitable solvent in this reaction is a reaction-inert solvent,
 10 such as an alcohol.

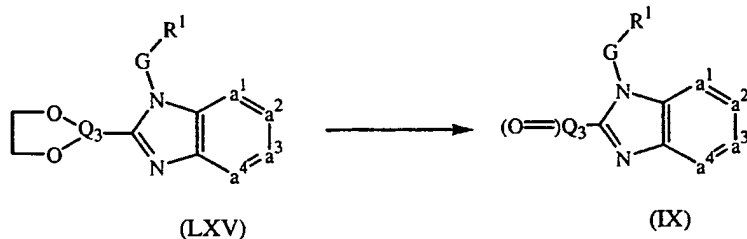


Intermediates of formula (LXII) can be prepared by deprotecting an intermediate of formula (LXIV) in the presence of a suitable acid, such as hydrochloric acid and the like, in a suitable solvent, e.g. water.
 15

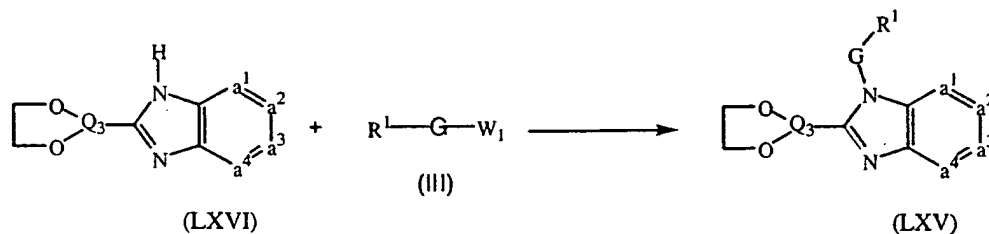


Intermediates of formula (IX) may be prepared by deprotecting an intermediate of formula (LXV) in the presence of a suitable acid, e.g. hydrochloric acid and the like.

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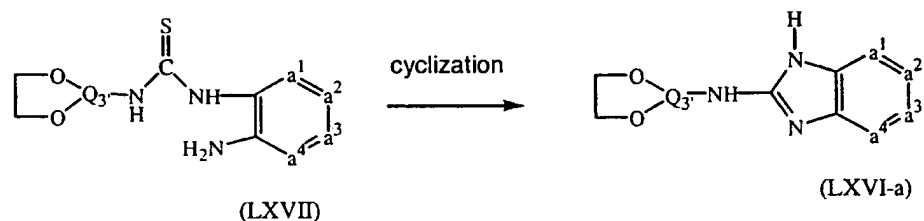
Intermediates of formula (LXV) can be prepared by reacting an intermediate of formula (LXVI) with an intermediate of formula (III) in the presence of a suitable base, e.g. dipotassium carbonate, in a suitable reaction-inert solvent, e.g. acetonitrile.



5

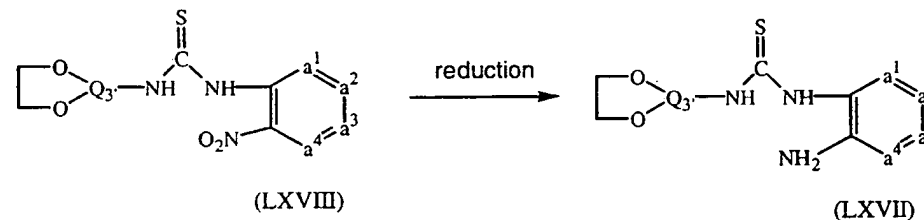
Intermediates of formula (LXVI) wherein, in the definition of Q₃, the X¹ or X² moiety of the radicals of formula (b-1) to (b-8) represent NH, said Q₃ being represented by Q₃-NH, and said intermediates being represented by formula (LXVI-a), may be prepared by cyclizing an intermediate of formula (LXVII) in the presence of mercury oxide and sulphur, in a suitable reaction-inert solvent, e.g. an alcohol.

10



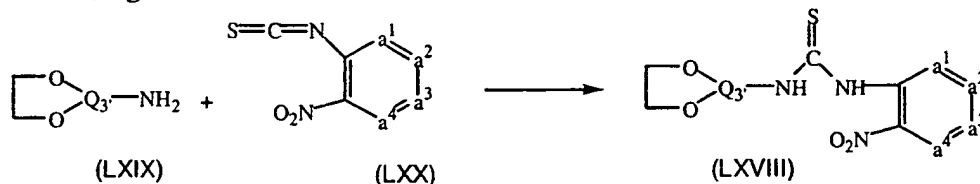
Intermediates of formula (LXVII) can be prepared by reducing an intermediate of formula (LXVIII) in the presence of a suitable reducing agent, such as hydrogen, in the presence of a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal and the like, in a suitable solvent, e.g. a mixture of ammonia in alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like.

15

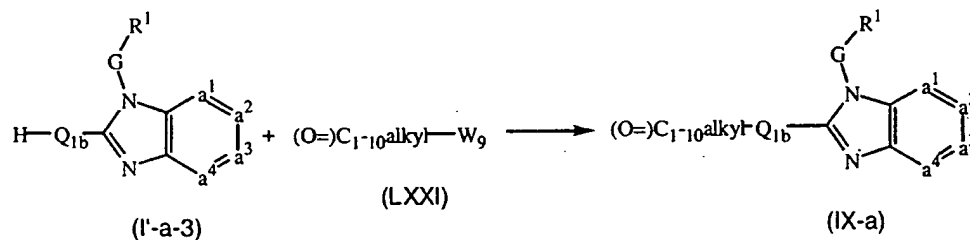


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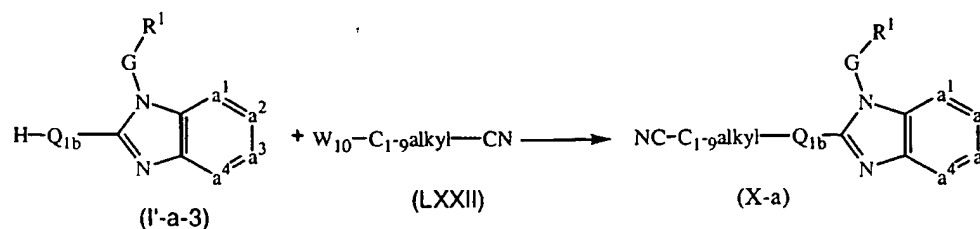
Intermediates of formula (LXVIII) can be prepared by reacting an intermediate of formula (LXIX) with an intermediate of formula (LXX) in a suitable reaction-inert solvent, e.g. ethanol.



- 5 Intermediates of formula (IX), wherein, in the definition of Q_3 , R^2 comprises $C_{1-10}alkyl$, said Q_3 being represented by $C_{1-10}alkyl-Q_{1b}$, and said intermediates being represented by formula (IX-a), can be prepared by reacting a compound of formula (I'-a-3) with a reagent of formula (LXXI), wherein $(O=)C_{1-10}alkyl$ represents a carbonyl derivative of $C_{1-10}alkyl$ and wherein W_9 is a suitable leaving group, such as a halo atom, e.g. bromo,
- 10 in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.

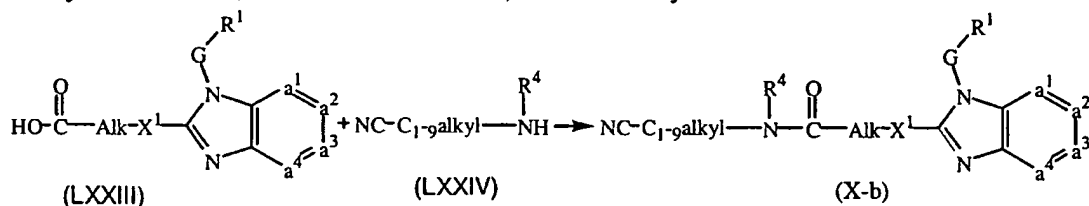


- Intermediates of formula (X) wherein Q_4 comprises $C_{1-9}alkyl$, said Q_4 being represented by $C_{1-9}alkyl-Q_{1b}$, and said intermediates being represented by formula (X-a), can be prepared by reacting a compound of formula (I'-a-3) with a reagent of formula (LXXII),
- 15 wherein W_{10} represents a suitable leaving group, such as a halo atom, e.g. chloro, in a reaction-inert solvent, e.g. 3-methyl-2-butanone, in the presence of a suitable base, e.g. dipotassium carbonate, sodium bicarbonate and the like.

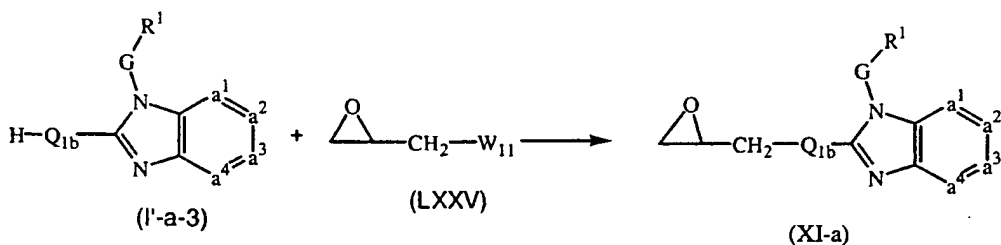


- 20 Intermediates of formula (X), wherein $NC-Q_4$ represents $NC-(C_{1-9}alkyl)(R^4)N-C(=O)-Alk-X^1$, said intermediates being represented by formula (X-b), can be prepared by reacting an intermediate of formula (LXXIII) with an intermediate of formula (LXXIV)

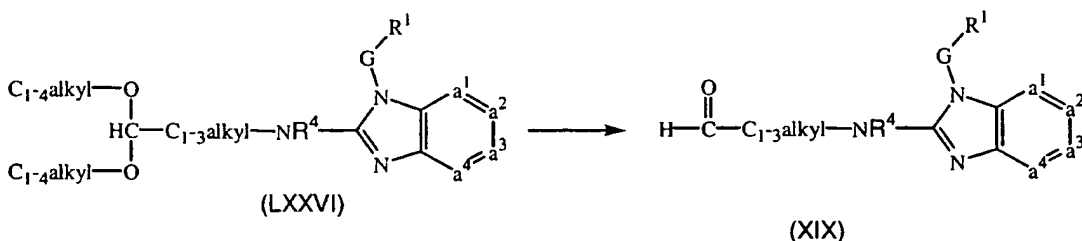
in the presence of di-1*H*-imidazol-2-yl-methanone, a suitable base, such as *N,N*-diethyl-ethanamine, and a suitable solvent, such as methylene chloride.



Intermediates of formula (XI), wherein Q_{1b} represents Q_{1b} , said intermediates being represented by formula (XI-a), can be prepared by reacting a compound of formula (I'-a-3) with an intermediate of formula (LXXV), wherein W_{11} represents a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as disodium carbonate, and in the presence of a suitable solvent, such as 3-methyl-2-butanone.



Intermediates of formula (XIX) can be prepared by reacting an intermediate of formula (LXXVI) with a suitable acid, such as hydrochloric acid.



Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid, respectively chiral base.

Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I), (I') or the compounds of group (I'') or any subgroup thereof, show antiviral properties. Viral infections treatable using the compounds and methods of the present invention include those infections brought on by ortho- and paramyxoviruses and in particular by human and bovine respiratory syncytial virus (RSV).

The *in vitro* antiviral activity against RSV of the present compounds was tested in a test as described in the experimental part of the description, and may also be demonstrated in a virus yield reduction assay. The *in vivo* antiviral activity against RSV of the present compounds may be demonstrated in a test model using cotton rats as described in Wyde et al. (Antiviral Research (1998), 38, 31-42).

Due to their antiviral properties, particularly their anti-RSV properties, the compounds of formula (I), (I') or the compounds of group (I'') or any subgroup thereof, their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, are useful in the treatment of individuals experiencing a viral infection, particularly a RSV infection, and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses, in particular the respiratory syncytial virus.

The compounds of formula (I') or the compounds of group (I'') or any subgroup thereof may therefore be used as medicines. In particular, the compounds of formula (I), (I') or the compounds of group (I'') may be used in the manufacture of a medicament for the treatment or the prevention of viral infections, especially RSV infections. The use as a medicine or method of treatment comprises the systemic administration to viral infected

subjects or to subjects susceptible to viral infections of an amount effective to combat the conditions associated with the viral infection, in particular the RSV infection.

The compounds of the present invention or any subgroup thereof may be formulated
5 into various pharmaceutical forms for administration purposes. As appropriate
compositions there may be cited all compositions usually employed for systemically
administering drugs. To prepare the pharmaceutical compositions of this invention, an
effective amount of the particular compound, optionally in addition salt form or as
metal complex, as the active ingredient is combined in intimate admixture with a
10 pharmaceutically acceptable carrier, which carrier may take a wide variety of forms
depending on the form of preparation desired for administration. These pharmaceutical
compositions are desirable in unitary dosage form suitable, particularly, for
administration orally, rectally, percutaneously, or by parenteral injection. For example,
in preparing the compositions in oral dosage form, any of the usual pharmaceutical
15 media may be employed such as, for example, water, glycols, oils, alcohols and the like
in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions
and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders,
disintegrating agents and the like in the case of powders, pills, capsules, and tablets.
Because of their ease in administration, tablets and capsules represent the most
20 advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are
obviously employed. For parenteral compositions, the carrier will usually comprise
sterile water, at least in large part, though other ingredients, for example, to aid
solubility, may be included. Injectable solutions, for example, may be prepared in
which the carrier comprises saline solution, glucose solution or a mixture of saline and
25 glucose solution. Injectable suspensions may also be prepared in which case
appropriate liquid carriers, suspending agents and the like may be employed. Also
included are solid form preparations which are intended to be converted, shortly before
use, to liquid form preparations. In the compositions suitable for percutaneous
administration, the carrier optionally comprises a penetration enhancing agent and/or a
30 suitable wetting agent, optionally combined with suitable additives of any nature in
minor proportions, which additives do not introduce a significant deleterious effect on
the skin.

The compounds of the present invention may also be administered via oral inhalation or
insufflation by means of methods and formulations employed in the art for
35 administration via this way. Thus, in general the compounds of the present invention
may be administered to the lungs in the form of a solution, a suspension or a dry
powder, a solution being preferred. Any system developed for the delivery of solutions,

suspensions or dry powders via oral inhalation or insufflation are suitable for the administration of the present compounds.

Thus, the present invention also provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising a compound
5 of formula (I') or a compound of the group (I'') and a pharmaceutically acceptable carrier. Preferably, the compounds of the present invention are administered via inhalation of a solution in nebulized or aerosolized doses.

It is especially advantageous to formulate the aforementioned pharmaceutical
10 compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated
15 tablets), capsules, pills, powder packets, suppositories, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

In general it is contemplated that an antivirally effective daily amount would be from 0.01 mg/kg to 500 mg/kg body weight, more preferably from 0.1 mg/kg to 50 mg/kg
20 body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

25 It may be appropriate to administer an antivirally effective daily dosage as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms.

The exact dosage and frequency of administration depends on the particular compound
30 of formula (I), (I') or a compound of group (I'') used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased
35 depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

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Also, the combination of another antiviral agent and a compound of formula (I), (I') or a compound of the group (I'') can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), (I') or a compound of the group (I''), and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in antiviral treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. For instance, the compounds of the present invention may be combined with interferon-beta or tumor necrosis factor-alpha in order to treat or prevent RSV infections.

The following examples are intended to illustrate the present invention.

Experimental part

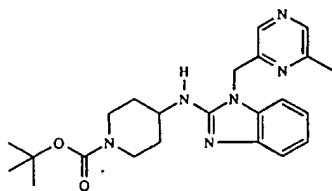
Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DIPE" is defined as diisopropylether, "DMSO" is defined as dimethylsulfoxide, and "THF" is defined as tetrahydrofuran.

Preparation of the intermediate compounds

Example A1

a) NaOCH₃ (0.2 mol) was added to a mixture of *N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine dihydrobromide (0.1 mol) in methanol (389ml), the mixture was cooled on an ice bath and stirred for 2 hours. Bis(1,1-dimethylethyl) dicarbonate (0.1mol) was added to a cooled mixture on an ice bath and then stirred for 18 hours at room temperature. The mixture was evaporated and suspended in water/DIPE. The residue was filtered off, washed with water/DIPE and dried. The residue was boiled up in CH₃OH. Yield : 17.46g of 1,1-dimethylethyl 4-(1*H*-benzimidazol-2-ylamino)-1-piperidinecarboxylate (55.2%) (interm. 1).

b) Preparation of



(interm. 2)

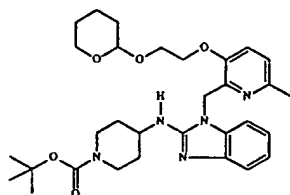
1-Bromo-2,5-pyrrolidinedione (0.055 mol) and then dibenzoyl peroxide (cat.quant.) were added to a mixture of 2,6-dimethylpyrazine (0.05 mol) in CCl₄ (100ml). The mixture was stirred and refluxed for 4 hours, stirred at room temperature under N₂ flow overnight, cooled on an ice bath and filtered. The filtrate was evaporated, to give residue 1. NaH (0.04 mol) was added to a solution of intermediate (1) (0.04 mol) in DMF (150ml). The mixture was stirred at room temperature under N₂ flow for 1 hour. Residue 1 was dissolved in DMF (50ml) and added dropwise to the mixture. The mixture was stirred at 50°C overnight. DMF was evaporated. The residue was taken

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up in H₂O and the mixture was extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated. Yield: 6.82g of intermediate (2) (32%).

Example A2

Preparation of

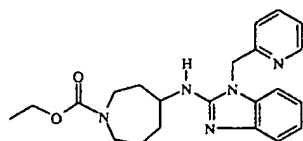


(interm. 3)

Reaction under N₂ flow. NaH 60% (0.02 mol) was added to a mixture of (±)-6-methyl-3-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]-2-pyridinemethanol (0.02 mol) in DMF (75ml). Methanesulfonyl chloride (0.02 mol) was added. The mixture was added at room temperature to a mixture of intermediate (1) (0.02 mol) and NaH (0.022 mol) in DMF (100ml), previously stirred at 40°C for 1 hour. The mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was taken up in H₂O and CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/ (CH₃OH/NH₃) 97/3). The pure fractions were collected and the solvent was evaporated. Yield: 3.52g of intermediate (3) (31%).

Example A3

Preparation of

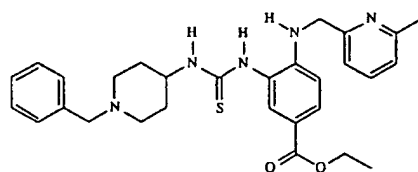


(interm. 4)

2-Chloro-1-(2-pyridylmethyl)-1H-benzimidazole (0.0615 mol) and ethyl 4-amino-hexahydro-1H-azepine-1-carboxylate (0.123 mol) were stirred at 160°C for 3 hours. H₂O was added and the mixture was extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (13.6g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 98/2/0.1). The pure fractions were collected and the solvent was evaporated. Yield: 10.5g of intermediate (4) (43%).

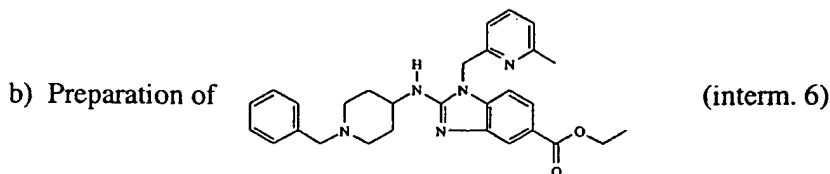
Example A4

a) Preparation of



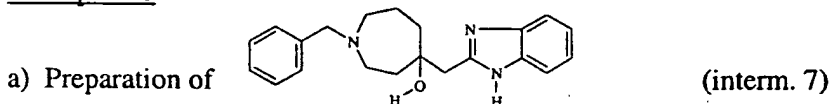
(interm. 5)

A mixture of ethyl 3-amino-4-[[[(6-methyl-2-pyridyl)methyl]amino]benzoate (0.166 mol) and 4-isothiocyanato-1-(phenylmethyl)piperidine (0.166 mol) in ethanol (500ml) was stirred and refluxed for 8 hours and at room temperature overnight. The precipitate was filtered off and used without further purification. Yield: intermediate (5).

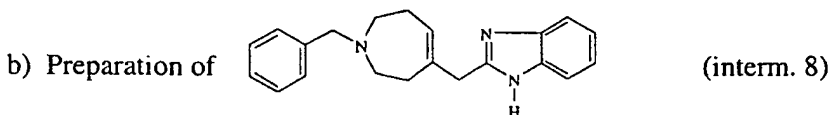


- 5 A mixture of intermediate (5) (0.16 mol), HgO (0.192 mol) and S (spat.tip) in DMF (100ml) was stirred at 80°C for 4 hours, filtered warm over dicalite, washed with warm DMF, heated again and filtered warm over dicalite. The solvent was evaporated. The residue was taken up in CH₂Cl₂. The mixture was washed with H₂O. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue
10 was co-evaporated with toluene. The residue was crystallized from CH₃CN. The precipitate was filtered off and dried. Yield: 53.5g of intermediate (6) (70%)

Example A5



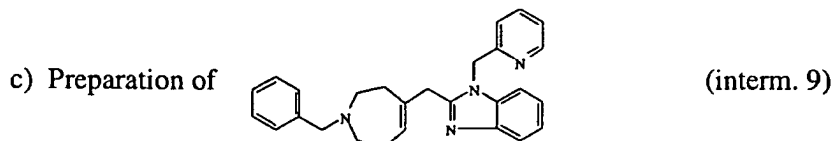
- A mixture of *N*-(1-methylethyl)-2-propanamine (0.098 mol) in THF (100ml) was stirred at -40°C under N₂ flow. BuLi 1.6M in hexane (0.098 mol) was added dropwise. The
15 mixture was stirred at -40°C for 30 min and cooled to -70°C. A mixture of 1-(diethoxymethyl)-2-methyl-1*H*-benzimidazole (0.098 mol) in THF (50ml) was added dropwise and the mixture was stirred for 45 minutes. A mixture of hexahydro-1-(phenylmethyl)-4*H*-azepin-4-one (0.049 mol) in THF (50ml) was added dropwise at -70°C. The mixture was hydrolyzed cold and extracted with EtOAc. The organic layer
20 was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated (yielding 7.5g). Part of the residue (3.5g) was crystallized from EtOAc. The precipitate was filtered off and dried. Yield: 2.3g of intermediate (7).



- 25 A mixture of intermediate (7) (0.029 mol) in 1,1'-oxybis[2-methoxyethane] (300ml) and H₂SO₄ conc. (20ml) was stirred at 160°C for 24 hours. Ice water was added. The mixture was basified with K₂CO₃ solid and extracted with CH₂Cl₂. The organic layer

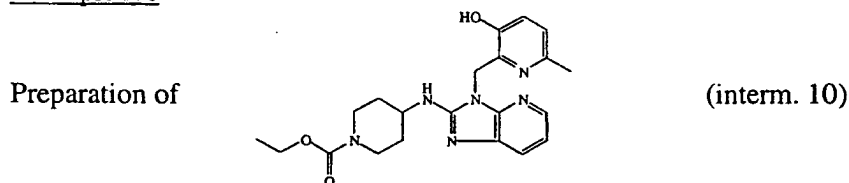
-50-

was separated, dried, filtered and the solvent was evaporated. Yield: 18g of a mixture of 2 compounds, of which one compound is intermediate (8) (75%).



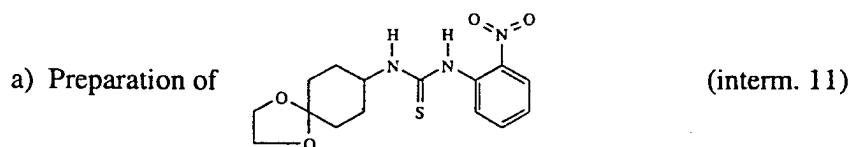
A mixture of intermediate (8), 2-(chloromethyl)pyridine (0.047 mol) and K_2CO_3 (0.0775 mol) in acetonitrile (500ml) was stirred and refluxed for 24 hours. H_2O was added and the mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried, filtered and the solvent was evaporated. Yield: 15.4g of a mixture of 2 compounds, of which one is intermediate (9).

Example A6

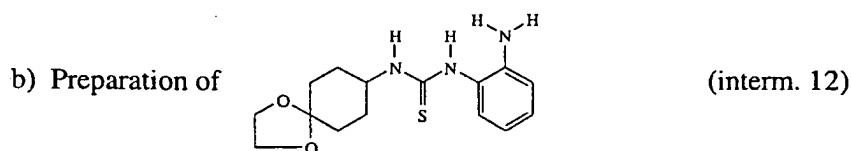


N,N-diethylethamine (16ml) and then 2-chloromethyl-6-methyl-3-pyridinol (0.0376 mol) were added to a mixture of ethyl 4-[(3*H*-imidazo[4,5-*b*]pyridin-2-yl)amino]-1-piperidinecarboxylate (0.0376 mol) in DMF (550ml). The mixture was stirred at room temperature for 3 hours and at 50°C overnight. The solvent was evaporated. The residue was poured out into H_2O and CH_2Cl_2 . The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH_2Cl_2/C_2H_5OH 95/5 to 70/30). The desired fraction was collected and the solvent was evaporated. Yield: 2.1 g of intermediate (10).

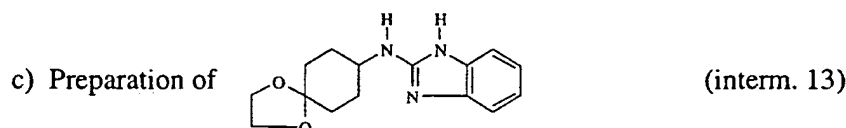
Example A7



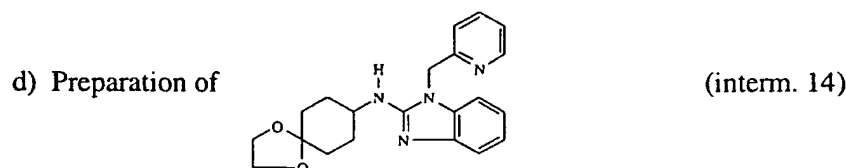
A mixture of 1,4-dioxaspiro[4,5]decan-8-amine (0.28 mol) and 1-isothiocyanto-2-nitrobenzene (0.28 mol) in ethanol (300ml) was stirred at room temperature for 2 hours. The solvent was evaporated. The product was used without further purification. Yield: 90g of intermediate (11).



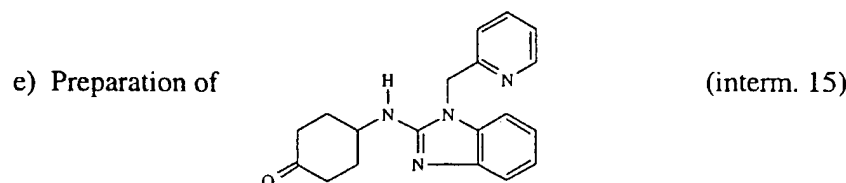
A mixture of intermediate (11) (0.178 mol) in $\text{NH}_3/\text{CH}_3\text{OH}$ (500ml) and THF (100ml) was hydrogenated at room temperature under a 3 bar pressure for 24 hours with Pd/C (52g) as a catalyst. After uptake of H_2 (3 equiv), the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated. The product was used without
5 further purification. Yield: 44g of intermediate (12).



A mixture of intermediate (12) (0.071 mol), HgO (0.142 mol) and S (0.56g) in ethanol (300ml) was stirred and refluxed for 4 hours, filtered over celite, washed with CH_2Cl_2 and the filtrate was evaporated. The reaction was carried out again using the same quantities. The residues were combined and then purified by column chromatography
10 over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 94/6/0.5; 20-45 μm). The pure fractions were collected and the solvent was evaporated. Yield: 14.5g of intermediate (13) (43%); mp. $>260^\circ\text{C}$.



A mixture of intermediate (13) (0.049 mol), 2-(chloromethyl)pyridine (0.0735 mol) and K_2CO_3 (0.196 mol) in acetonitrile (325ml) was stirred and refluxed for 4 hours and then
15 brought to room temperature. The reaction was carried out again using the same quantities. The mixtures were combined. H_2O was added and the mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 98/2/0.1; 20-45 μm). The pure fractions
20 were collected and the solvent was evaporated. Part of this fraction (0.6g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.46g of intermediate (14); mp. 136°C .

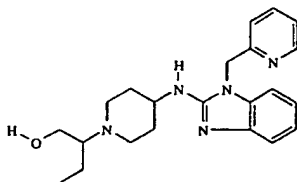


A mixture of intermediate (14) (0.077 mol) in HCl 3N (350ml) was stirred and refluxed for 1 hour, poured out into ice water, basified with K_2CO_3 solid and extracted with
25 CH_2Cl_2 . The organic layer was separated, washed with H_2O , dried (MgSO_4), filtered

and the solvent was evaporated. Part of the residue (1.5g) was crystallized from CH₃CN and diethyl ether. The precipitate was filtered off and dried. Yield: 0.5g of intermediate (15); mp. 148°C.

Example A8

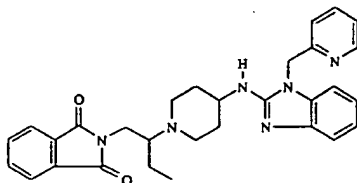
a) Preparation of



(interm. 16)

- 5 LiAlH₄ (0.023 mol) was added portionwise at 5°C to a solution of (±)-ethyl α-ethyl-4-[[1-(2-pyridylmethyl)-1H-benzimidazol-2-yl]amino]-1-piperidineacetate (0.021 mol) in THF (100ml). The mixture was stirred at 5°C for 1 hour. EtOAc was added. The mixture was hydrolyzed with ice water, filtered over celite, washed with EtOAc, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 7.2g of intermediate (16)
 10 (88%).

b) Preparation of

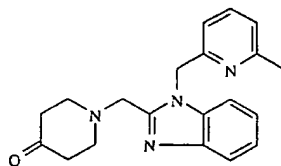


(interm. 17)

- Diethyl azodicarboxylate (0.028 mol) was added slowly at room temperature to a solution of intermediate (16) (0.019 mol), 1H-isoindole-1,3(2H)-dione (0.028 mol) and triphenyl phosphine (0.028 mol) in THF (200ml). The mixture was stirred at room temperature for 8 hours. The solvent was evaporated till dryness. The residue was
 15 dissolved in CH₂Cl₂. The solution was acidified with HCl 3N, basified with NH₄OH and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (12g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/ CH₃OH/NH₄OH 97/3/0.1; 20-45 μm). The pure fractions were collected and the solvent was evaporated. Yield: 5.5g of intermediate
 20 (17) (57%).

Example A9

a) Preparation of

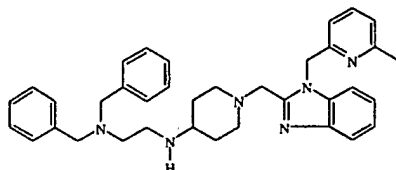


(interm. 18)

A mixture of 8-[[1-[(6-methyl-2-pyridyl)methyl]-1H-benzimidazol-2-yl]methyl]-1,4,8-dioxaspiro[4.5]decane (0.0196 mol) in HCl 6N (55ml) and H₂O (55ml) was

stirred and refluxed for 6 hours. Toluene was added. The mixture was poured out on ice, alkalized with a NaOH solution and extracted with CH_2Cl_2 . The organic layer was separated, dried, filtered and the solvent was evaporated. Part of this fraction was suspended in DIPE, filtered off and dried. Yield: 0.32g of intermediate (18) (91%).

b) Preparation of

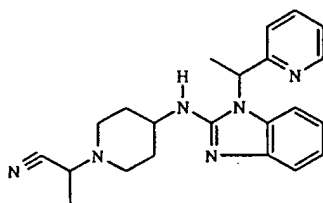


(interm. 19)

- 5 A mixture of intermediate (18) (0.008 mol) and *N,N*-dibenzylethylenediamine (0.01 mol) in methanol (150ml) was hydrogenated with Pd/C 10% (1g) as a catalyst in the presence of thiophene solution (0.5ml). After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. Yield: 5.39g of intermediate (19) (quant.).

Example A10

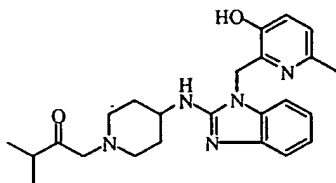
a) Preparation of



(interm. 20)

- 10 A mixture of (\pm)-*N*-(4-piperidiny)-1-[1-(2-pyridyl)ethyl]-1*H*-benzimidazol-2-amine (0.026 mol), 2-chloropropanenitrile (0.039 mol) and K_2CO_3 (0.052 mol) in acetonitrile (100ml) was stirred and refluxed for 8 hours. H_2O was added and the mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (8.5g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 96/4; 20-45 μm). The pure fractions
- 15 were collected and the solvent was evaporated. Yield: 4.5g of intermediate (20) (46%).

b) Preparation of

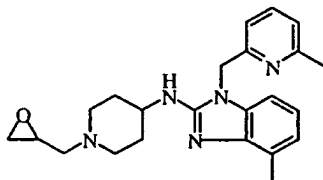


(interm. 22)

- A mixture of compound 49 (0.0164 mol), 1-bromo-3-methyl-2-butanone (0.03 mol) and K_2CO_3 (0.06 mol) in CH_3CN (100ml) was stirred and refluxed for several hours. H_2O was added. The solvent was evaporated. 4-Methyl-2-pentanone was added. The
- 20 organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/(\text{CH}_3\text{OH}/\text{NH}_3)$ 98/2). The desired fractions were collected and the solvent was evaporated. Yield: 2.75g of intermediate (22) (40%).

Example A11

Preparation of

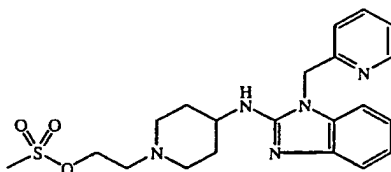


(interm. 21)

A mixture of compound 90 (0.015 mol), (chloromethyl)oxirane (0.008 mol) and Na_2CO_3 (1.59g) in 4-methyl-2-pentanone (150ml) was heated slowly to 100°C (to 40°C in 1 hour, 70°C in 1 hour), stirred at 100°C overnight, then stirred and refluxed for 20 hours. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/(\text{CH}_3\text{OH}/\text{NH}_3)$ 95/5). Two fractions were collected and their solvents were evaporated. Fraction 1 was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 0.18g of intermediate (21).

Example A12

a) Preparation of

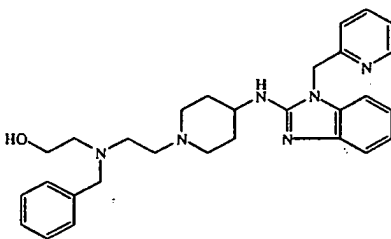


(interm. 23)

Methylsulfonyl chloride (0.0512 mol) was added dropwise at 0°C under N_2 flow to a mixture of 4-[[1-(2-pyridinylmethyl)-1H-benzimidazol-2-yl]amino]-1-piperidineethanol (0.0256 mol) and *N,N*-diethylethanamine (0.0512 mol) in CH_2Cl_2 (200ml). The mixture was stirred at room temperature for 90 minutes. The solvent was evaporated till dryness.. Yielding: intermediate (23)

15

b) Preparation of



(interm. 24)

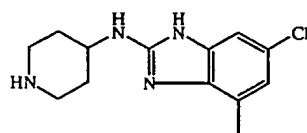
A mixture of intermediate (23) (0.028 mol), 2-[(phenylmethyl)amino]ethanol, (0.034 mol) and K_2CO_3 (0.112 mol) in CH_3CN (200ml) was stirred at 60°C for 4 hours. H_2O was added and the mixture was extracted with ethyl acetate. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (13.5g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 97/3/0.5; 35-70 μm). The pure fractions were collected and the solvent was evaporated. Yield: 5.5g of intermediate (24) (41%).

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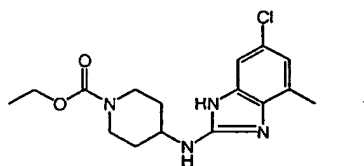
Example A13

Preparation of



(interm. 25)

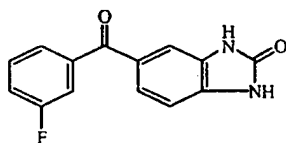
HCl 12N (165ml) was added to a mixture of



(interm. 36), prepared according to example A7c), (0.049 mol) in H₂O (165ml). The mixture was stirred and refluxed for 6 hours. The solvent was evaporated. HBr 48% (320ml) was added. The mixture was stirred and refluxed for 4 hours and then stirred overnight. The solvent was evaporated. 2-Propanol was added and the solvent was evaporated again. The residue was suspended in DIPE. The mixture was decanted, taken up in H₂O/DIPE and then separated into its layers. CH₂Cl₂ was added to the aqueous layer. The mixture was alkalinized with NH₄OH. 2-Propanol was added. The organic layer was separated, dried, filtered and the solvent was evaporated. Yield: 15g of intermediate (25).

Example A14

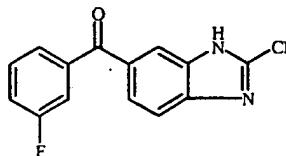
a) Preparation of



(interm. 26)

3,4-diaminophenyl-(3-fluorophenyl)methanone (0.056 mol) and urea (0.084 mol) were stirred at 150 à 160°C for 4 hours (melt) and then cooled. Water was added. The mixture was stirred at 50°C for a while and then cooled. The precipitate was filtered off, stirred in 2-propanone and dried. Yield: 11.4g of intermediate (26).

b) Preparation of



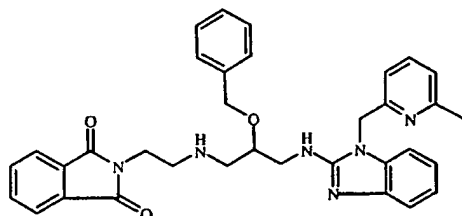
(interm. 27)

Phosphorus oxychloride (50ml) was added carefully to intermediate (26) (0.045 mol). The mixture was stirred and refluxed for 24 hours and then was stood at room temperature over the weekend. The solvent was evaporated. The residue was taken up in CH₂Cl₂/ice/K₂CO₃ solid. The mixture was separated into its layers. The aqueous layer was extracted with CH₂Cl₂. The undissolved material was filtered off to give residue 1. The combined organic layer was dried, filtered and the solvent was evaporated to give residue 2. Residue 1 and residue 2 were combined. Yield: 16.75g

of intermediate (27) (100%).

Example A15

Preparation of



(interm. 28)

A mixture of compound (341) (0.0025 mol), prepared according to B25a), 2-(2-bromoethyl)-1*H*-Isoindole-1,3(2*H*)-dione (0.00275 mol) and K₂CO₃ (3g) in CH₃CN (100ml) was stirred and refluxed for 24 hours. The solvent was evaporated. The residue was dissolved in CH₂Cl₂ and then washed with water. The organic layer was dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₃) 97/3). The pure fractions were collected and the solvent was evaporated. Yield: intermediate (28).

10

Example A16

a) 2, 4,5-trimethyloxazole (0.225mol) was stirred in CCl₄ (500mL) under N₂-flow. Then 1-bromo-2,5-pyrrolidinedione (0.225mol) and benzoyl peroxide (cat.quant.) were added. This mixture was stirred and refluxed for 1hour under N₂-flow. The reaction mixture was cooled in an ice bath (ice/salt). The mixture was filtered. The filtrate was evaporated. Yield: 42.7g (<100%) of 5-(bromomethyl)-2,4-dimethyloxazole (intermediate 30).

15

b) Intermediate (30) (0.225 mol) was taken up in DMF (450ml). Na[N(CH(=O))₂] (0.225 mol) was added portionwise and the mixture was stirred at 50°C for 1hour and at room temperature overnight. The mixture was evaporated. Yield : 41g (100%) of *N*-[(2,4-dimethyl-5-oxazolyl)methyl]-*N*-formylformamide (intermediate 31).

20

c) A mixture of intermediate (31) (0.225 mol) in HCl 36% (120ml) and ethanol (500ml) was refluxed for 1hour and stirred overnight. The mixture was filtered off, the precipitate was washed with C₂H₅OH and the filtrate was evaporated. The residue was taken up in ice water, alkalized with NaOH and extracted with CH₂Cl₂. The mixture was separated and the organic layer was dried and evaporated. Yield : 28g (100%) of 2,4-dimethyl-5-oxazolmethanamine (intermediate 32).

25

d) 2-chloro-3-nitropyridine (0.225 mol) and Na₂CO₃ (0.225 mol) were added to a mixture of intermediate (32) (0.225 mol) in ethanol (500ml) and the mixture was stirred and refluxed for 6hours. The mixture was evaporated and the residue was taken up in water and extracted with CH₂Cl₂. The mixture was separated and the organic layer was

30

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dried, filtered off and evaporated. The residue was purified by column chromatography over silica gel. The pure fractions were collected and evaporated. Yield : 27g (48%) of *N*-[(2,4-dimethyl-5-oxazolyl)methyl]-3-nitro-2-pyridinamine (intermediate 33).

e) A mixture of intermediate (33) (0.1 mol) was hydrogenated in a thiophene solution
 5 4% (3ml) and methanol (400ml) with Pd/C 5% (4g) as a catalyst. After uptake of H₂ (3eq), the catalyst was filtered off. The residue was evaporated and used without further purification. Yield : 21.8 g (100%) of *N*²-[(2,4-dimethyl-5-oxazolyl)methyl]-2,3-pyridinediamine (intermediate 34).

f) Intermediate (34) (0.1 mol) was dissolved in DMF (250ml). Ethyl 4-isothiocyanato-
 10 1-piperidinecarboxylate (0.1 mol) was added and the mixture was stirred at 50°C for 20 hours. HgO (0.125 mol) and sulfur powder (few crystals) were added and the mixture was stirred at 75°C for 3hours 30minutes. The mixture was filtered over dicalite and the filtrate was evaporated. The residue was taken up in water/CH₂Cl₂. The mixture was separated, the organic layer was dried, filtered off and evaporated. The residue was
 15 purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 95/5). The pure fractions were collected and evaporated. The residue was crystallized from DIPE and recrystallized from CH₃CN. Yield : 216.6277g (55.4%) of ethyl 4-[[3-[(2,4-dimethyl-5-oxazolyl)methyl]-3*H*-imidazo[4,5-*b*]pyridin-2-yl]amino-1-piperidinecarboxylate (intermediate 35).

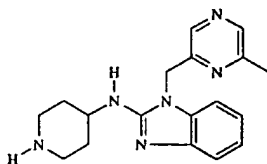
20 Example A17

Cl-CH₂-C(=NH)-O-C₂H₅ (0.0625 mol) was added to a mixture of *N*²-[(2-methyl-5-oxazolyl)methyl]-2,3-pyridinediamine (0.05 mol) in acetic acid (150mL) and the mixture was stirred for 20 hours at room temperature. The mixture was warmed up to 90°C and stirred for 10 minutes at this temperature. The mixture was evaporated at
 25 <50°C. The residue was taken up in water/CH₂Cl₂ + Na₂CO₃. The organic layer was separated, extracted with CH₂Cl₂, dried (MgSO₄) and filtered. The residue was taken up in DIPE + active charcoal and stirred for 1hour. The mixture was filtered and evaporated, Yield : 13.1 g (100%) of 2-(chloromethyl)-3-[(2-methyl-5-oxazolyl)methyl]-3*H*-imidazo[4,5-*b*]pyridine (intermediate 29). Preparation of the final

30 compounds

Example B1

a) Preparation of

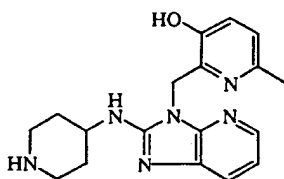


(compound 1)

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A mixture of intermediate (2) (0.016 mol) in 2-propanol/HCl (10ml) and 2-propanol (100ml) was stirred and refluxed for 2 hours and then cooled. The precipitate was filtered off, washed with DIPE and dried. The residue was taken up in H₂O, NH₃ and CH₃OH and the mixture was extracted with CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/(CH₃OH/NH₃) 90/10). The pure fractions were collected and the solvent was evaporated. Yield: 1.8g of compound (1) (35%).

b) Preparation of

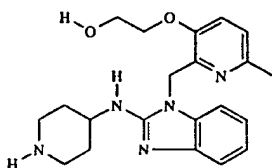


(compound 308)

A mixture of intermediate (10) (0.0054 mol) in HBr 48% (50 ml) was stirred and refluxed for 5 hours. The solvent was evaporated. The residue was suspended in DIPE, filtered off and crystallized from ethanol. The solvent was evaporated and the fraction was purified by high-performance liquid chromatography over RP Hyperprep (eluent: (0.5% NH₄OAc in H₂O)/CH₃CN from 100/0 to 0/100). The pure fractions were collected and the solvent was evaporated. Yield: 0.188 g of compound (308).

Example B2

a) Preparation of



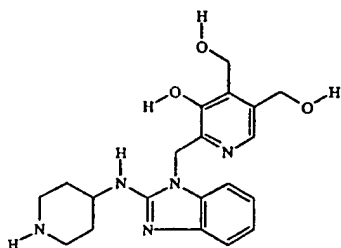
(compound 2)

HCl (1:3); H₂O (1:2)

A mixture of intermediate (3) (0.00622 mol) in 2-propanol/HCl (10ml) and 2-propanol (100ml) was stirred and refluxed for 4 hours. The solvent was evaporated. The residue was taken up in H₂O, Na₂CO₃ and CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was dissolved in 2-propanol and DIPE and converted into the hydrochloric acid salt with 2-propanol/HCl. The precipitate was filtered off and dried. This fraction was converted into the free base and purified over silica gel on a glass filter (eluent: CH₂Cl₂/(CH₃OH/NH₃) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was converted into the hydrochloric acid salt (1:3). The precipitate was filtered off and dried. Yield: 0.65g of compound (2) (20%).

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b) Preparation of



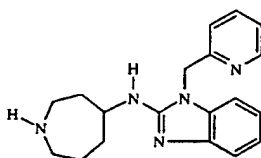
(compound 3)

HCl (1:3); H₂O (1:2)

A mixture of 1,1-dimethylethyl 4-[[1-[[3,5-dihydro-3,3-dimethyl-9-(phenylmethoxy)-1*H*-[1,3]dioxepino[5,6-*c*]pyridin-2-yl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (0.00552 mol) in HCl 10N (200ml) was stirred and refluxed for 6 hours. The solvent was evaporated. The residue was suspended in DIPE, filtered off and dried. Yield: 0.58g of compound (3).

Example B3

Preparation of

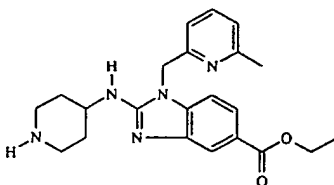


(compound 4)

A mixture of intermediate (4) (0.021 mol) and KOH (0.43 mol) in 2-propanol (100ml) was stirred and refluxed overnight. H₂O was added and the mixture was extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 6.9g of compound (4) (quant.).

Example B4

Preparation of



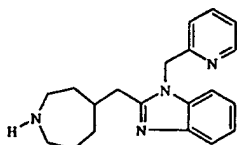
(compound 5)

A mixture of intermediate (6) (0.02 mol) in ethanol (120ml) was hydrogenated with Pd/C 10% (2g) as a catalyst. After uptake of H₂ (1 equiv), the catalyst was filtered off and the filtrate was evaporated, yielding a residue of 8g (100%). Part of this fraction (0.7g) was dissolved in ethanol and converted into the hydrochloric acid salt (1:3) with 2-propanol/HCl. DIPE was added. The mixture was stirred. The precipitate was filtered off and dried. Yield: 0.65g of compound (5).

Example B5

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Preparation of

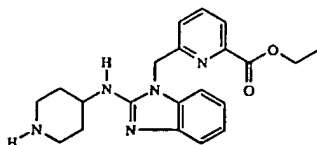


(compound 6)

A mixture of intermediate (9) (0.035 mol) in methanol (200ml) was hydrogenated at room temperature under a 3 bar pressure for 48 hours with Pd/C (1.5g) as a catalyst, then hydrogenation was continued at 40°C under a 3 bar pressure for 48 hours. After uptake of H₂ (2 equiv), the catalyst was filtered through celite and the filtrate was
 5 evaporated. The residue (12g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/ NH₄OH 80/20/3). The pure fractions were collected and the solvent was evaporated. Yield: 3.8g of compound (6) (34%).

Example B6

Preparation of

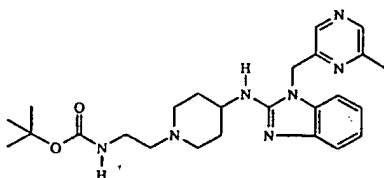


(compound 7)

A mixture of 6-[[2-(4-piperidinylamino)-1H-benzimidazol-1-yl]methyl]-2-pyridine-
 10 carboxylic acid in HCl 36% (5ml) and ethanol (50ml) was stirred and refluxed overnight. The solvent was evaporated. H₂O, NaHCO₃ and CH₂Cl₂ were added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/(CH₃OH/NH₃) 90/10). The
 15 pure fractions were collected and the solvent was evaporated. Yield: 0.83g of compound (7).

Example B7

Preparation of

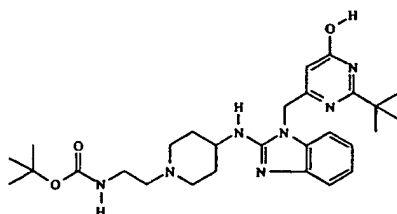


(compound 8)

A mixture of compound (1) (0.003 mol), 1,1-dimethylethyl (2-bromoethyl) carbamate (0.004 mol) and Na₂CO₃ (0.004 mol) in 2-butanone (100 ml) was stirred and refluxed overnight. The reaction mixture was cooled, washed with water and the layers were
 20 separated. The organic phase was washed with a NH₄Cl solution. The aqueous phase was extracted with CH₂Cl₂. The combined organic layers were dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/(CH₃OH/NH₃) 97/3). The pure fractions were collected and the solvent was evaporated. Yield: a residue of 1.18 g of compound (8) (84%).

Example B8

Preparation of

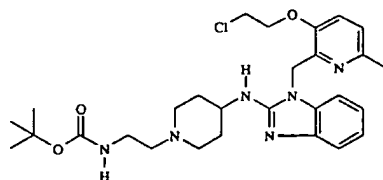


(compound 9)

Reaction under N₂ flow. NaH (0.01 mol) was added to a mixture of 1,1-dimethylethyl [2-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.01 mol) in DMF p.a. dry (100ml). The mixture was stirred at room temperature for 4 hours. 6-chloromethyl-2-(1,1-dimethylethyl)-4-pyrimidinol (0.01 mol) in a small amount of DMF p.a. dry was added dropwise. The mixture was stirred at 50°C overnight and then cooled. H₂O (50ml) was added. The solvent was evaporated. The residue was taken up in CH₂Cl₂. The organic solution was washed with H₂O/HOAc, dried (MgSO₄), filtered and the solvent was evaporated, to give residue 1. The aqueous layer was taken up in HOAc and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated, to give residue 2. Residue 1 and 2 were combined and purified by column chromatography over RP 18 BDS (eluent: NH₄OAc (0.5% in H₂O)/ CH₃OH/CH₃CN 70/15/15, 0/50/50 and 0/0/100). The pure fractions were collected and the solvent was evaporated. Yield: compound (9).

15 Example B9

a) Preparation of

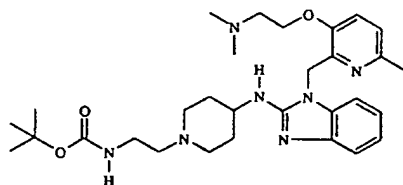


(compound 10)

Thionyl chloride (0.03 mol) was added to a mixture of (±)-6-methyl-3-[2-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethoxy]-2-pyridinemethanol (0.015 mol) in CH₂Cl₂ (100ml). Toluene was added and evaporated again. The residue was taken up in DMF (50ml) and then added to a mixture of 1,1-dimethylethyl [2-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.015 mol) and NaH (0.06 mol) in DMF (200ml). The mixture was stirred at 50°C overnight. The solvent was evaporated. The residue was taken up in H₂O and CH₂Cl₂. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/ (CH₃OH/NH₃) 99/1). The pure fractions were collected and the solvent was evaporated. The residue was suspended in petroleum ether. The precipitate was filtered off and dried. Yield: 1.55g of compound (10) (20%).

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b) Preparation of

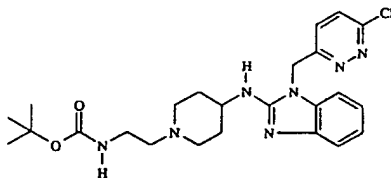


(compound 11)

A mixture of compound (10) (0.00147 mol) and $\text{NH}(\text{CH}_3)_2$ gas (20g) in THF (100ml) was stirred at 125°C for 16 hours. The solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: $\text{CH}_2\text{Cl}_2/(\text{CH}_3\text{OH}/\text{NH}_3)$ 95/5). The pure fractions were collected and the solvent was evaporated. Yield: 0.43g of compound (11) (53%).

Example B10

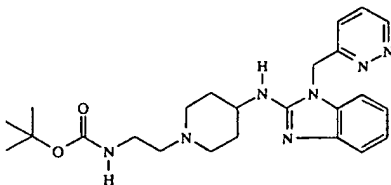
a) Preparation of



(compound 12)

1-Bromo-2,5-pyrrolidinedione (0.088 mol) and then dibenzoyl peroxide (cat.quant.) were added to a solution of 3-chloro-6-methylpyridazine (0.08 mol) in CCl_4 (mol. sieves) (200ml). The mixture was stirred and refluxed for 6 hours and then filtered over dicalite. 1-Bromo-2,5-pyrrolidinedione (0.088 mol) and dibenzoyl peroxide (cat.quant.) were added again. The mixture was stirred and refluxed overnight and filtered over dicalite. The solvent was evaporated at a temperature below 40°C . The residue was dissolved in DMF (70ml) and added to a mixture of 1,1-dimethylethyl [2-[4-(1H-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.0214 mol) and NaH (0.0235 mol) in DMF (190ml), previously stirred at room temperature for 1 hour and at 40°C for 1 hour. The resulting mixture was stirred at 50°C overnight. The solvent was evaporated. H_2O and CH_2Cl_2 were added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/(\text{CH}_3\text{OH}/\text{NH}_3)$ 97/3). The pure fractions were collected and their solvents were evaporated. Yield: 1.21g of compound (12).

b) Preparation of

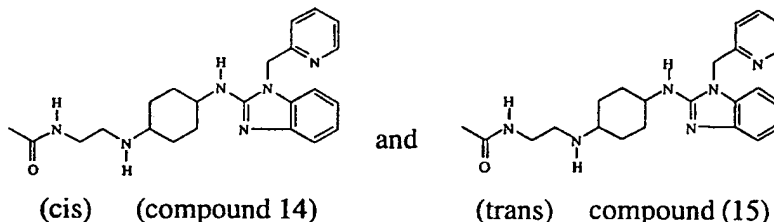


(compound 13)

A mixture of compound (12) (0.0025 mol), CaO (2g) and Pd/C (1g) in 1-butanethiol (2ml) and THF (100ml) was stirred at room temperature for the weekend. The solvent was evaporated. Yield: 1g of compound (13) (88%).

Example B11

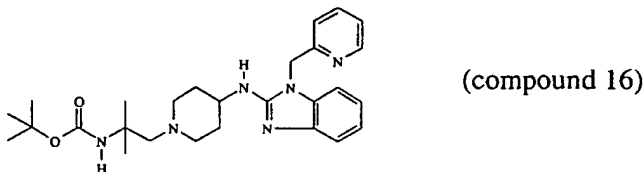
Preparation of



- 5 A mixture of intermediate (15) (0.031 mol) and *N*-(2-aminoethyl)acetamide (0.093 mol) in methanol (300ml) was hydrogenated at 30°C under a 3 bar pressure for 12 hours with Pd/C (5g) as a catalyst. After uptake of H₂ (1 equiv), the catalyst was filtered through celite, washed with CH₃OH and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/ CH₃OH/NH₄OH 92/8/0.5;
10 20-45 µm). Two pure fractions were collected and their solvents were evaporated, yielding a residue of 2.8g (22%) and 9g (71%). Parts of these fractions (0.6g; 0.8g) were crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.52g of compound (14); mp. 126°C and 0.53g of compound (15); mp. 200°C.

Example B12

Preparation of

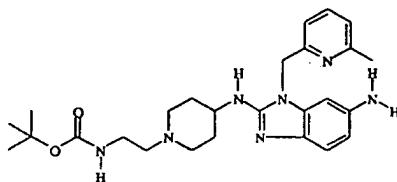


- 15 NaBH₃CN (0.048 mol) was added portionwise at 5°C to a solution of *N*-4-piperidinyl-1-(2-pyridylmethyl)-1*H*-benzimidazol-2-amine dihydrochloride (0.032 mol) and 1,1-dimethylethyl (1,1-dimethyl-2-oxoethyl)carbamate (0.032 mol) in methanol (100ml). The mixture was stirred at room temperature for 8 hours and hydrolyzed at 5°C with ice water. Methanol was evaporated. The residue was extracted with CH₂Cl₂.
20 The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (13g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/ NH₄OH 95/5/0.1; 20-45 μm). The pure fractions were collected and the solvent was evaporated. Yield : 2.2g of compound (16) (14%).

Example B13

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Preparation of

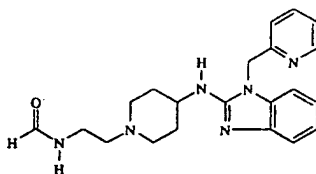


(compound 17)

A mixture of 1,1-dimethylethyl [2-[4-[[1-[(6-methyl-2-pyridyl)methyl]-6-nitro-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.0084 mol) in methanol (150ml) was hydrogenated at 50°C with Pt/C 5% (1g) as a catalyst in the presence of thiophene solution (1ml). After uptake of H₂ (3 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/(CH₃OH/NH₃) 99/1 to 97.5/2.5). The pure fractions were collected and the solvent was evaporated. Yield: 3.3g of compound (17) (82%).

Example B14

Preparation of

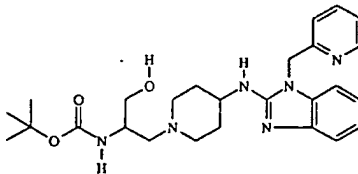


(compound 18)

A mixture of *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-pyridyl)methyl]-1H-benzimidazol-2-amine (0.143 mol) in HCOOH (50ml) was stirred and refluxed for 3 hours. The solvent was evaporated till dryness. The residue was dissolved in CH₂Cl₂. The mixture was basified with Na₂CO₃, filtered and the filtrate was evaporated till dryness. The residue (4.9g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 92/8/1; 20-45 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone. The precipitate was filtered off and dried. Yield: 2.8g of compound (18) (51%); mp. 146°C.

Example B15

Preparation of



(compound 19)

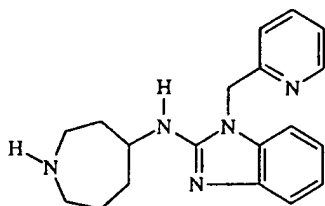
LiAlH₄ (0.0065 mol) was added portionwise at 5°C to a solution of (±)-1,1-dimethylethyl [1-(methoxycarbonyl)-2-[4-[[1-(2-pyridylmethyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.0059 mol) in THF (30ml). The mixture was stirred at 5°C for 1 hour. EtOAc was added. The mixture was hydrolyzed with ice water, filtered over celite and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.8g) was purified by column

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chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 92/8/0.5; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yield: 1.55g of compound (19) (56%).

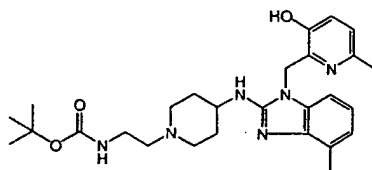
Example B16

a) Preparation of



(compound 290)

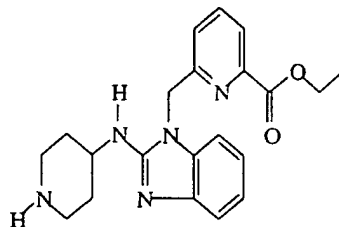
A mixture of



(0.021mol) in 2-propanol/HCl

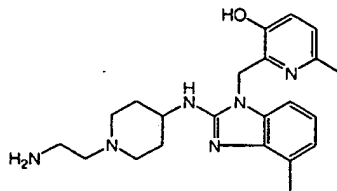
- 5 (29 ml) and 2-propanol (290 ml) was stirred and refluxed for 2 hours and then cooled to room temperature. The precipitate was filtered off and combined with analogously obtained fraction. The precipitate was dissolved at reflux in ethanol (150 ml), then allowed to crystallize out. The precipitate was filtered off and dried (45 °C, 16 hours, then air-dried for 30 minutes). Yield: 8.9 g (70%) of compound (290). Compound
10 (290) was converted into the free base according to art known procedures resulting in compound (355).

b) Preparation of



(compound 356) and

preparation of



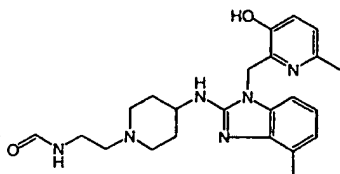
(compound 357).

Hydroxybutanedioate (1:1) Hydrate (1:2)

- Compound (355) (0.001 mol) was added to ethanol (6 ml; absolute ethanol) and heated to reflux temperature to give an homogeneous solution (I). Solution (I) was treated with butanedioic acid (0.118 g, 0.001 mol) and resulted in immediate salt formation. The
15 mixture was heated to reflux temperature, became homogeneous, then was allowed to

cool to room temperature. The precipitate was filtered off, and dried (vacuum, 50 °C, 24 hours). Yield: 0.40 g (78%) of compound (356). Solution (I) was treated with hydroxybutanedioic acid (0.134 g, 0.001 mol) and the mixture was heated to reflux temperature, became homogeneous, then was allowed to cool to room temperature. The precipitate was filtered off and dried (vacuum, 50 °C, 24 hours). Yield: 0.46 g (87%) of compound (357).

c) Preparation of



(compound 354)

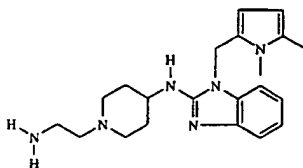
Compound (290) (0.000065 mol) was dissolved in water (3 ml). The mixture was stirred and alkalized with concentrated NH_4OH (400 μl , and 100 μl). CHCl_3 (20 ml) was added. The mixture was stirred vigorously for 10 minutes. More conc. NH_4OH (100 μl) was added and the mixture was stirred vigorously for 5 minutes. The organic layer was separated, then the alkalic layer was re-extracted once with CHCl_3 (5 ml). The combined organic layers were washed once with a saturated aqueous NaCl solution, then dried (MgSO_4), filtered and the solvent was evaporated. The residue was stirred in HCOOH (20 ml) until complete dissolution (= after 2 minutes). Acetic acid anhydride (0.00213 mol) was added dropwise over 1 minute and the reaction mixture was stirred at room temperature. After 24 hours, more acetic acid anhydride (50 μl) was added and the reaction mixture was stirred for 15 minutes. More acetic acid anhydride (50 μl) was added to the reaction mixture. The whole was stirred for 2 hours 15 minutes on a 60 °C oil-bath, then stood over the weekend at room temperature. More acetic acid anhydride (1000 μl) was added to the reaction mixture. The whole was stirred for 30 minutes on a 60-70 °C oil-bath, then stirred overnight at room temperature. Again, the reaction mixture was stirred for 2.5 hours at 60 °C. More acetic acid anhydride (100 μl) was added and the reaction mixture was stirred for 45 minutes at 60 °C, then stood overnight at room temperature. Water (100 μl) was added to decompose remaining acetic acid anhydride. The solvent was evaporated (in vacuo at 60 °C). Toluene was added to the residue, then evaporated again (in vacuo, 60 °C). Xylene was added, then evaporated (in vacuo at 60 °C) to give (x). To a sample, water (3 drops) was added. NH_4OH (10 μl) was added. Water (5 drops) was added and the mixture was shaken vigorously to give (y). (x) and (y) were dissolved in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/(\text{CH}_3\text{OH}/\text{NH}_3)$ 84/12/4, then purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/(\text{CH}_3\text{OH}/\text{NH}_3)$ 84/12/4). The product fractions were collected and the solvent was evaporated. This fraction (0.185 g) was stirred in boiling

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ethanol (± 10 ml), allowed to cool to room temperature, then Et₂O (10 ml) was added and the mixture was stirred for 15 minutes. The precipitate was filtered off by suction, rinsed with Et₂O, then air-dried for 3 hours, then dried further (high vacuum, 2 hours at room temperature, then air-dried overnight at room temperature). Yield: 0.153 g of compound (354).

Example B17

Preparation of



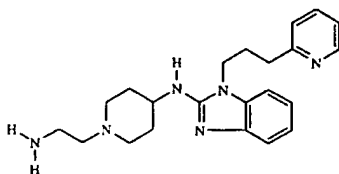
(compound 21)

H₂O (1:1)

A mixture of 1,1-dimethylethyl [2-[4-[[1-(1,5-dimethyl-1H-pyrrol-2-yl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.002 mol) and KOH (1g) in sec. butanol (25ml) was stirred and refluxed for 1 hour. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/ (CH₃OH/NH₃) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was suspended in DIPE. The precipitate was filtered off and dried. Yield: 0.57g of compound (21).

Example B18

Preparation of



(compound 22)

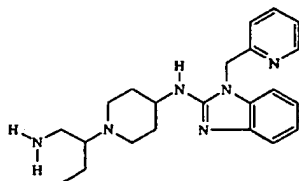
HCl (1:4); H₂O (1:2)

A mixture of 2-[2-[4-[[1-[3-(2-pyridyl)propyl]-1H-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-1H-isoindole-1,3(2H)-dione (0.005 mol) in HCl 6N (120ml) and HOAc (60ml) was stirred and refluxed for 30 hours and then cooled on an ice bath. A NaOH solution was added carefully dropwise until pH > 7. The mixture was extracted with CH₂Cl₂ and then separated into its layers. The aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with H₂O, separated again, dried (MgSO₄), filtered and the solvent was evaporated. The residue was taken up in a small amount of 2-propanol and converted into the hydrochloric acid salt (1:4) with 2-propanol/HCl 6N. DIPE was added. The precipitate was filtered off, washed with DIPE and dried. Yield: 1.95g of compound (22) (70%).

Example B19

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Preparation of

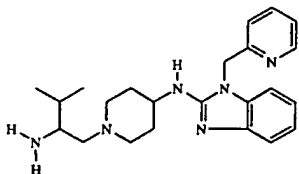


(compound 23)

- A mixture of intermediate (17) (0.01 mol) in hydrazine (5ml) and ethanol (50ml) was stirred and refluxed for 30 minutes. The solvent was evaporated. The residue was dissolved in CH_2Cl_2 . The organic solution was washed with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue (4.8g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 89/10/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 51.7g of compound (23) (45%); mp. 112°C.

Example B20

Preparation of

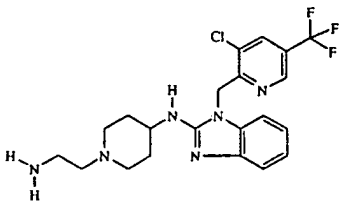


(compound 24)

- A mixture of 3-methyl-1-[4-[[1-(2-pyridylmethyl)-1H-benzimidazol-2-yl]amino]-1-piperidinyl]-2-butanone (0.01 mol) and benzenemethanamine (0.031 mol) in methanol (50ml) was hydrogenated at 40°C under a 3 bar pressure for 24 hours with Pd/C (0.4g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered through celite, washed with CH_3OH and CH_2Cl_2 and the filtrate was evaporated. The residue (5g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 93/7/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from pentane. The precipitate was filtered off and dried. Yield: 1g of compound (24) (21%); mp. 115°C.

Example B21

Preparation of



(compound 25)

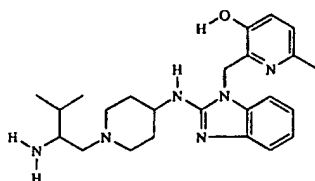
- Reaction under N_2 atmosphere. Na_2CO_3 (0.250 g) was added to 1,1-dimethylethyl [2-[4-(1H-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.0028 mol) in DMF (10 ml). The mixture was stirred for 4 hours at room temperature. The reaction mixture was divided over 5 tubes. 2-Chloromethyl-3-chloro-5-trifluoropyridine

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- (0.100 g) was added to each tube and the resulting reaction mixture was stirred overnight at 50 °C. The mixture was acidified with HCl/2-propanol, then stirred for 3 hours at 90°C. The mixture was alkalized with NH₃/CH₃OH and the desired compound was isolated and purified by high-performance liquid chromatography over a Prochrom D.A.C.-column with Hypersil 'BDS' HS C18 (100 g, 8 µm, 100 Å; eluent gradient: ((0.5% NH₄OAc in H₂O)/CH₃OH/CH₃CN (0 min) 70/15/15, (10.31 min) 0/50/50, (16.32 min) 0/0/100, (16.33 min-end) 70/15/15). The desired fractions were collected and the solvent was evaporated. Yield: 0.020 g of compound (25).

Example B22

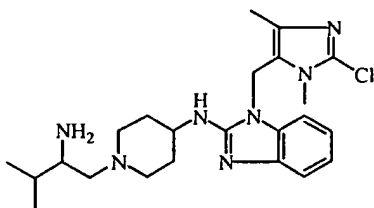
a) Preparation of



(compound 26)

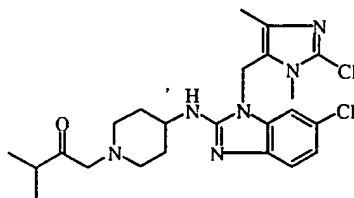
- A mixture of 1-[4-[[1-[(3-hydroxy-6-methyl-2-pyridyl)methyl]-1H-benzimidazol-2-yl]-amino]-1-piperidiny]-3-methyl-2-butanone (0.0065 mol) in CH₃OH/NH₃ (300ml) was hydrogenated at room temperature with Rh/Al₂O₃ (1g) as a catalyst in the presence of CH₃OH/NH₃ (3ml). After uptake of H₂ (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/(CH₃OH/NH₃) 95/5 to 90/10). The pure fractions were collected and the solvent was evaporated. Yield: 1.52g of compound (26) (55%).

b) Preparation of

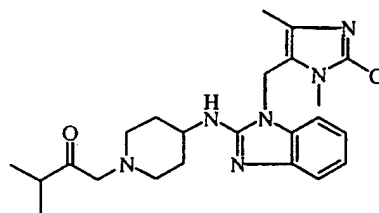


(compound 298)

A mixture
(0.6g) of



and



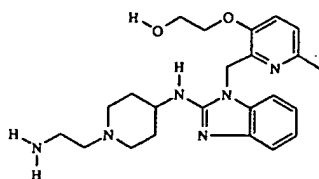
- (prepared analogous to the procedure described in example A10b)) in NH₃/CH₃OH (100 ml) was hydrogenated for 16 hours at 50°C with Rh/C (0.5 g) as a catalyst in the presence of thiophene solution (1 ml). After uptake of H₂ (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by high-performance liquid chromatography over Kromasil C18 (100 Å; eluent: NH₄OAc 0.5%

-70-

H₂O/CH₃CN 75%, 25% CH₃OH to CH₃CN 100%). Two pure fraction groups were collected and their solvent was evaporated. Yield : 0.165 g of compound 298.

Example B23

Preparation of



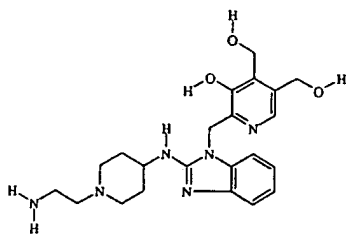
(compound 27)

HCl (1:3); H₂O (1:1)

A mixture of (±)-1,1-dimethylethyl [2-[4-[[1-[[[6-methyl-3-[2-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethoxy]-2-pyridyl]methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-carbamate (0.0014 mol) in 2-propanol/HCl (5ml) and 2-propanol (50ml) was stirred and refluxed for 4 hours and taken up in H₂O, Na₂CO₃ and CH₂Cl₂. The organic layer was separated. 2-Propanol/HCl (5ml) and 2-propanol (50ml) were added again. The mixture was stirred and refluxed for 1 hour and converted into the hydrochloric acid salt. The precipitate was filtered off and dried. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/ (CH₃OH/NH₃) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was converted into the hydrochloric acid salt. The precipitate was filtered off and dried. Yield: 0.18g of compound (27) (23%).

15 Example B24

Preparation of



(compound 28)

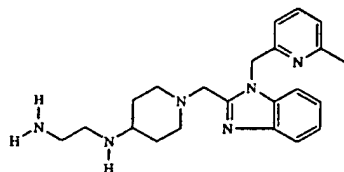
HCl (1:1)

A mixture of 1,1-dimethylethyl [2-[4-[[1-[[[3,5-dihydro-3,3-dimethyl-9-(phenylmethoxy)-1*H*-[1,3]dioxepino[5,6-*c*]pyridin-2-yl]methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.00213 mol) in HCl 10N (100ml) was stirred and refluxed for 4 hours. The solvent was evaporated. The residue was suspended in DIPE. The precipitate was filtered off and dried. Yield: 0.9g of compound (28).

Example B25

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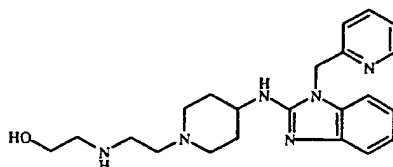
a) Preparation of



(compound 29)

A mixture of intermediate (19) (0.008 mol) in methanol (150ml) was hydrogenated with Pd/C (1g) as a catalyst. After uptake of H₂ (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/ (CH₃OH/NH₃) 95/5, 93/7 to 90/10). The pure fractions were collected and the solvent was evaporated. Yield: 1.81g of compound (29) (60%).

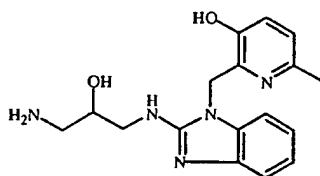
b) Preparation of



(compound 312)

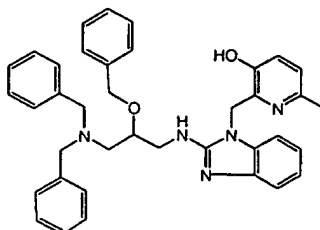
A mixture of intermediate (24) (0.011 mol) in methanol (100ml) was hydrogenated at room temperature under a 3 bar pressure overnight with Pd/C (2g) as a catalyst. The catalyst was recuperated and hydrogenation was continued at room temperature under a 3 bar pressure for 2 hours with Pd/C (2g) as a catalyst. After uptake of hydrogen (1 equiv), the catalyst was filtered off, washed with CH₃OH and CH₂Cl₂ and the filtrate was evaporated. The residue (4.5g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 85/15/1 and 56/40/4; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanol and diethyl ether. The precipitate was filtered off and dried. Yield: 1.8g of compound (312) (40%).

c) Preparation of



(compound 313)

A mixture of



(0.016 mol), prepared

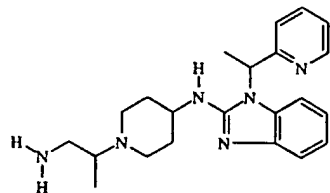
according to A5c), in methanol (250 ml) was hydrogenated with Pd/C 10% (2 g) as a catalyst. After uptake of hydrogen (3 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel

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(eluent: $\text{CH}_2\text{Cl}_2/(\text{CH}_3\text{OH}/\text{NH}_3)$ 90/10). The product fractions were collected and the solvent was evaporated. Yield: 4.2 g of compound (313).

Example B26

Preparation of

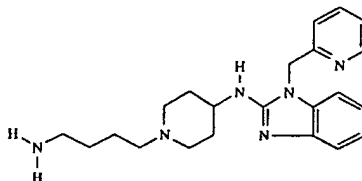


(compound 30)

- 5 LiAlH_4 (0.014 mol) was added portionwise at 5°C to a solution of intermediate (20) (0.012 mol) in THF (50ml). The mixture was allowed to warm to room temperature and then stirred at room temperature for 48 hours. EtOAc was added. The mixture was hydrolyzed with ice water, filtered over celite, washed with EtOAc and the filtrate was extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and
- 10 the solvent was evaporated. The residue (3g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 87/13/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 0.75g of compound (30) (16%); mp. 85°C .

15 Example B27

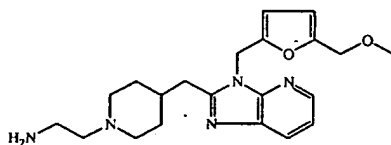
a) Preparation of



(compound 31)

- A mixture of 4-[[1-(2-pyridylmethyl)-1H-benzimidazol-2-yl]amino]-1-piperidinebutanenitrile (0.01 mol) in $\text{CH}_3\text{OH}/\text{NH}_3$ (80ml) was hydrogenated at room temperature under a 3 bar pressure overnight with Raney Nickel (3.8g) as a catalyst. After uptake of H_2 (2 equiv), the catalyst was filtered through celite and the filtrate was evaporated.
- 20 The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 2.9g of compound (31) (76%); mp. 94°C .

b) Preparation of



(compound 314)

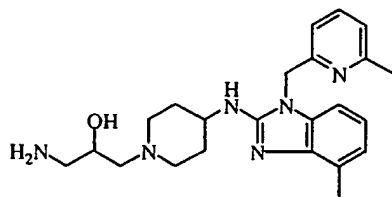
A mixture of 5-[[2-[[1-(2-aminoethyl)-4-piperidinyl]methyl]-3H-imidazo[4,5-b]pyridin-3-yl]methyl]-2-furanmethanol (0.0068 mol) in $\text{CH}_3\text{OH}/\text{NH}_3$ (300 ml) was

hydrogenated at 20 °C with Raney Nickel (1 g) as a catalyst. After uptake of H₂ (2 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/(CH₃OH/NH₃) from 95/5 to 90/10). The desired fractions were collected and the solvent was evaporated.

- 5 The residue was repurified by column chromatography over silica gel (eluent: CH₂Cl₂/(CH₃OH/NH₃) 95/5). The purest fractions were collected and the solvent was evaporated. The residue was taken up into HCl/2-propanol and DIPE was added. The resulting salt was filtered off and purified by column chromatography over silica gel (eluent: CH₂Cl₂/(CH₃OH/NH₃) 98/2). The pure fractions were collected and the solvent
10 was evaporated. Yield: 0.2 g of compound (314).

Example B28

Preparation of

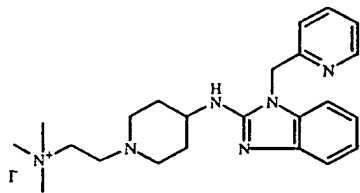


(compound 303)

- A mixture of intermediate 21 (0.001 mol) in CH₃OH/NH₃ (100ml) was stirred at room temperature for 20 hours and at 100°C for 16 hours. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/ (CH₃OH/NH₃) 90/10). The pure fractions were collected and the solvent was
15 evaporated. The residue was dried. Yield: 0.11g of compound 303.

Example B29

Preparation of



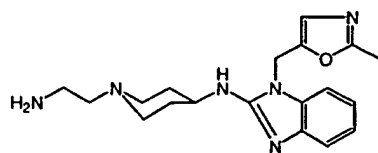
(compound 315)

- Iodomethane (0.00494 mol) was added at room temperature to a solution of compound (328) (0.004491 mol) in 2-propanone (17ml), and the reaction mixture was stirred at
20 room temperature for 1 hour. The precipitate was filtered off and dried. The residue (1.6g) was crystallized from 2-propanone. The precipitate was filtered off and dried. Yield: 1.5g of compound (315) (64%).

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Example B30

Preparation of

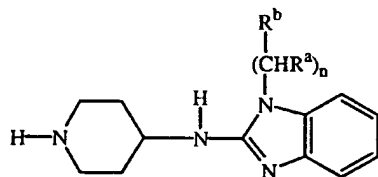


(compound 316)

Hydrochloride (1:3) Hydrate (1:1)

Compound (317) (0.0027 mol) was dissolved in ethanol (50ml). The mixture was converted into the hydrochloric acid salt (1:3) with 2-propanol/HCl. The precipitate was filtered off and dried. Yield: 1.68g of compound (316).

Tables 1 to 17 list the compounds of formula (I') and the compounds of group (I'') which were prepared according to one of the above examples.

10 Table 1

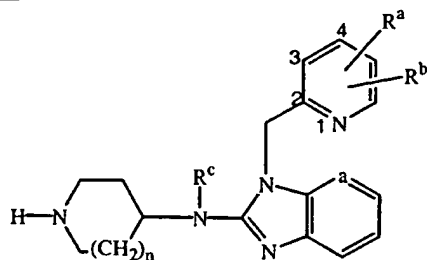
Co. No.	Ex. No.	n	R ^a	R ^b	Physical data
32	B1a	1	H	1,4-dimethyl-1H-imidazol-5-yl	H ₂ O (1:2)
33	B1a	1	H	1,4-dimethyl-5-[COOC ₂ H ₅]-1H-imidazol-2-yl	HCl (1:3)
34	B1a	1	H	2-bromo-5-pyridyl	
35	B1a	1	CH ₃	2-pyrazinyl	
36	B1a	1	ethyl	2-pyrazinyl	
37	B1a	1	H	2-pyridyl	HCl (1:2); mp. >160°C
38	B1a	1	CH ₃	2-pyridyl	
39	B1a	2	H	2-pyridyl	HCl (1:3); H ₂ O (1:2)
40	B1b	2	H	2-pyridyl	
41	B1b	3	H	2-pyridyl	HBr (1:3)
42	B1a	0	-	2-pyrimidinyl	
43	B1a	1	H	2-pyrimidinyl	HCl (1:3); H ₂ O (1:1)
44	B1a	1	H	3,5,6-trimethyl-2-pyrazinyl	
45	B1a	1	H	3-[C ₂ H ₅ -O-(CH ₂) ₂ -O]-6-methyl-2-pyridyl	HCl (1:3); H ₂ O (1:3)
46	B1a	1	H	3-amino-2-pyridyl	HCl (1:3); H ₂ O (1:2)

Co. No.	Ex. No.	n	R ^a	R ^b	Physical data
47	B1a	1	H	3-amino-2-pyridyl	
48	B1a	1	H	3-hydroxy-2-pyridyl	HCl (1:3); H ₂ O (1:1)
49	B1a	1	H	3-hydroxy-6-methyl-2-pyridyl	HCl (1:3); H ₂ O (1:3)
50	B1a	1	H	3-hydroxy-6-pyridaziny	HCl (1:2); H ₂ O (1:1)
51	B1a	1	H	3-methoxy-6-methyl-2-pyridyl	HCl (1:3); H ₂ O (1:2)
52	B1a	1	H	3-methoxy-6-methyl-2-pyridyl	
53	B1a	1	H	3-methyl-2-pyraziny	
3	B2b	1	H	3-OH-4,5-(-CH ₂ -OH) ₂ -2-pyridyl	HCl (1:3); H ₂ O (1:2)
54	B1a	1	H	3-pyridaziny	
55	B3	1	H	1,5-(CH ₃) ₂ -1H-pyrrol-2-yl	
56	B1a	1	H	4,6-dimethyl-2-pyridyl	
57	B1a	1	H	4-chloro-2-pyridyl	
58	B1a	1	H	4-methoxy-2-pyridyl	
59	B1a	1	H	4-methyl-1H-imidazol-5-yl	HCl (1:3); H ₂ O (1:1)
60	B1a	1	H	4-pyridyl	HCl (1:3); H ₂ O (1:1)
61	B1a	1	H	4-pyridyl	
62	B1a	1	H	4-pyrimidiny	
63	B1a	1	H	5-chloro-1-methyl-1H-imidazol-2-yl	
64	B1a	1	H	5-methyl-2-pyraziny	HCl (1:1)
65	B1a	1	H	5-methyl-2-pyraziny	
66	B1a	1	H	6-(-CH ₂ -O-CH ₃)-2-pyridyl	HCl (1:2); H ₂ O (1:3)
67	B1a	1	H	6-(hydroxymethyl)-2-pyridyl	
68	B1a	1	H	6-[-CO-N(CH ₃) ₂]-2-pyridyl	
69	B1a	1	H	6-bromo-2-pyridyl	HCl (1:2)
70	B1a	1	H	6-bromo-2-pyridyl	
71	B1a	1	H	6-chloro-2-pyridyl	HCl (1:2)
72	B1a	1	H	6-HOOC-2-pyridyl	
73	B1a	1	CH ₃	6-hydroxymethyl-2-pyridyl	HCl (1:3); H ₂ O (1:1)
74	B1a	1	H	6-methoxy-2-pyridyl	
1	B1a	1	H	6-methyl-2-pyraziny	
75	B1a	1	CH ₃	6-methyl-2-pyraziny	
2	B2a	1	H	6-methyl-3-[-O-(CH ₂) ₂ -OH]-2-pyridyl	HCl (1:3); H ₂ O (1:2)
76	B1a	1	H	6-methyl-3-[-O-(CH ₂) ₂ -N(CH ₃) ₂]-2-pyridyl	HCl (1:4); H ₂ O (1:1)

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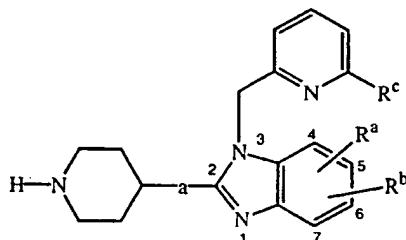
Co. No.	Ex. No.	n	R ^a	R ^b	Physical data
7	B6	1	H	6-(-COOC ₂ H ₅)-2-pyridyl	

Table 2



Co. No.	Ex. No.	n	a	R ^a	R ^b	R ^c	Physical data
78	B1a	1	CH	H	H	CH ₃	-
4	B3	2	CH	H	H	H	-
81	B16	1	CH	H	H	-CH ₂ -phenyl	-
308	B1b	1	N	3-OH	6-CH ₃	H	-

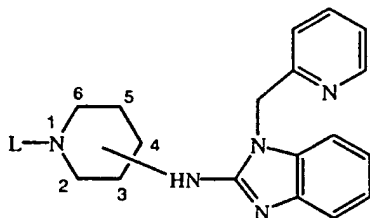
5 Table 3



Co. No.	Ex. No.	a	R ^a	R ^b	R ^c	Physical data
82	B4	CH ₂	5-OCH ₃	6-OCH ₃	H	
83	B1b	NH	5-Cl	6-Cl	CH ₃	HBr (1:3)
84	B1b	NH	5-CH ₃	6-CH ₃	CH ₃	HBr (1:3)
85	B1b	NH	4-Cl	H	CH ₃	HBr (1:3)
86	B1b	NH	7-Cl	H	CH ₃	HBr (1:3); H ₂ O (1:1)
87	B1b	NH	6-NO ₂	H	CH ₃	HBr (1:3); H ₂ O (1:1)
88	B1b	NH	7-CH ₃	H	CH ₃	HBr (1:3)
89	B1b	NH	5-NO ₂	H	CH ₃	HBr (1:3); H ₂ O (1:1)
90	B1b	NH	7-CH ₃	H	CH ₃	
91	B1b	NH	4-CH ₃	H	CH ₃	HBr (1:3)
92	B1b	NH	4-CH ₃	H	CH ₃	

Co. No.	Ex. No.	a	R ^a	R ^b	R ^c	Physical data
93	B1b	NH	5-CF ₃	H	CH ₃	HCl (1:3); H ₂ O (1:1) HCl (1:3); H ₂ O (1:2) HCl (1:4); H ₂ O (1:1)
94	B1b	NH	6-CF ₃	H	CH ₃	
95	B1b	NH	6-Cl	H	CH ₃	
96	B1b	NH	5-Cl	H	CH ₃	
5	B4	NH	6-(-COOC ₂ H ₅)	H	CH ₃	
97	B4	NH	6-(-COOC ₂ H ₅)	H	CH ₃	
98	B4	NH	6-(-CH ₂ -OH)	H	CH ₃	
99	B4	NH	6-(-CH ₂ -OH)	H	CH ₃	
100	B1a	CH[N(CH ₃) ₂]	H	H	CH ₃	

Table 4



Co. No.	Ex. No.	*	L	Physical data
101	B4	4	3-piperidinyl	HCl (1:4); H ₂ O (1:2) mp. 146°C
102	B4	3	H	
18	B14	4	-(CH ₂) ₂ -NH-CHO	
103	B7	4		HCl (1:4); H ₂ O (1:2); mp. 226°C HCl (1:3); H ₂ O (1:2); mp. 195°C HCl (1:4); H ₂ O (1:2); mp. 200°C mp. 112°C (A); mp. 106°C (B); mp. 98°C mp. 116°C mp. 168°C mp. 133°C mp. 112°C mp. 128°C
104	B16	4		
105	B16	4	-CH ₂ -C(CH ₃) ₂ -NH ₂	
106	B16	4	-CH ₂ -CH(CH ₂ OH)-NH ₂	
23	B19	4	-CH(C ₂ H ₅)-CH ₂ -NH ₂	
107	B19	4	-CH(C ₆ H ₅)-CH(C ₆ H ₅)-NH ₂	
108	B19	4	-CH(C ₆ H ₅)-CH(C ₆ H ₅)-NH ₂	
109	B19	4	2-aminocyclohexyl	
110	B19	4	-CH(phenylmethyl)-CH ₂ -NH ₂	
111	B19	4	-CH[C(CH ₃) ₃]-CH ₂ -NH ₂	
112	B19	4	-CH[CH ₂ -N(CH ₃) ₂]-CH ₂ -NH ₂	
113	B19	4	-CH ₂ -CH(NH ₂)-phenyl	

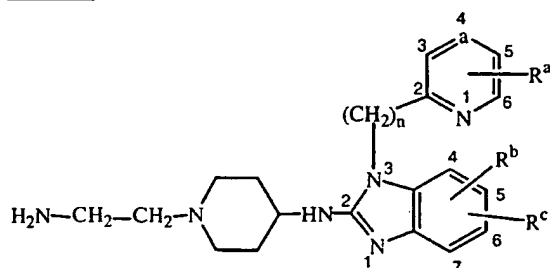
Co. No.	Ex. No.	*	L	Physical data
114	B19	4	-CH[CH ₂ -(1-piperidiny)]-CH ₂ -NH ₂	HCl (1:4); mp. 203°C
115	B19	4	-CH ₂ -CH(cyclopropyl)-NH ₂	H ₂ O (1:2); mp. 84°C
24	B20	4	-CH ₂ -CH[CH(CH ₃) ₂]-NH ₂	mp. 115°C
116	B20	4	-CH ₂ -CH(CH ₃)-NH ₂	H ₂ O (1:1)
117	B20	4	-CH(CH ₃)-CH(CH ₃)-NH ₂	(B); mp. 114°C
118	B20	4	-CH ₂ -CH(C ₂ H ₅)-NH ₂	mp. 140°C
119	B20	4	-CH ₂ -CH(cycloC ₆ H ₁₁)-NH ₂	mp. 134°C
120	B20	4	-CH(CH ₃)-CH(CH ₃)-NH ₂	(A); HCl (1:4); H ₂ O (1:4); mp. 214°C
121	B20	4	-CH ₂ -CH(NH ₂)-CH ₂ -CH(CH ₃) ₂	mp. 124°C
122	B20	4	-CH ₂ -CH(NH ₂)-(CH ₂) ₃ -CH ₃	mp. 142°C
123	B20	4	-CH ₂ -CH(NH ₂)-(CH ₂) ₂ -CH(CH ₃) ₂	mp. 152°C
124	B20	4	-CH ₂ -CH(NH ₂)-(CH ₂) ₂ -CH ₃	mp. 146°C
125	B20	4	-CH ₂ -CH(NH ₂)-(CH ₂) ₇ -CH ₃	mp. 136°C
126	B20	4	-CH ₂ -CH(NH ₂)-(CH ₂) ₂ -phenyl	mp. 136°C
127	B20	4	-CH ₂ -CH(NH ₂)-CH ₂ -C(CH ₃) ₃	HCl (1:4); H ₂ O (1:1); mp. 244°C
128	B20	4	-CH ₂ -CH(NH ₂)-CH(CH ₃)(C ₂ H ₅)	(A); H ₂ O (1:1); mp. 80°C
129	B20	4	-CH ₂ -CH(NH ₂)-CH(CH ₃)(C ₂ H ₅)	(B); mp. 90°C
130	B20	4	-CH ₂ -CH(NH ₂)-(CH ₂) ₂ -(4-methoxyphenyl)	mp. 100°C
131	B1a	4	-CH ₂ -CH(NH ₂)-(4-piperidiny]	HCl (1:5); H ₂ O (1:1); mp. 269°C
31	B27a	4	-(CH ₂) ₄ -NH ₂	mp. 94°C
132	B27a	4	-CH(CH ₃)-CH ₂ -NH ₂	mp. 142°C
133	B27a	3	-(CH ₂) ₂ -NH ₂	H ₂ O (1:1); mp. 90°C
134	B16	4	-(CH ₂) ₃ -NH ₂	HCl (1:4); H ₂ O (1:1); mp. >250°C
328	B7	4	-(CH ₂) ₂ -N(CH ₃) ₂	-
327	B7	4	-(CH ₂) ₂ -N(CH ₃) ₂	HCl (1:4); H ₂ O (1:3); mp. 180°C

* = position piperidiny]

(A) indicates the first isolated stereoisomeric form

(B) indicates the second isolated stereoisomeric form

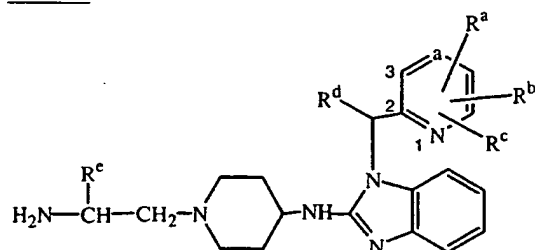
Table 5



Co. No.	Ex. No.	n	a	R ^a	R ^b	R ^c	Physical data
135	B1a	1	CH	6-[-COOCH(CH ₃) ₂]	H	H	
136	B1a	1	CH	6-[-COOC ₂ H ₅]	H	H	
137	B16	1	CH	6-CH ₂ OH	H	H	
138	B16	1	CH	6-CH ₃	5-Cl	6-Cl	HCl (1:4); H ₂ O (1:1)
139	B16	1	N	3-CH ₃	H	H	HCl (1:3); H ₂ O (1:1)
20	B16	1	N	6-CH ₃	H	H	HCl (1:3); H ₂ O (1:2)
140	B16	1	N	5-CH ₃	H	H	HCl (1:4); H ₂ O (1:2)
141	B16	2	CH	H	H	H	HCl (1:4); H ₂ O (1:1)
142	B16	1	CH	6-CH ₃	5-CH ₃	6-CH ₃	HCl (1:4); H ₂ O (1:2); 2-propanolate (1:1)
143	B16	1	CH	6-CH ₃	4-Cl	H	HCl (1:4); H ₂ O (1:2)
144	B16	1	CH	6-CH ₃	7-Cl	H	HCl (1:4); H ₂ O (1:2)
145	B16	1	CH	6-CH ₃	6-NO ₂	H	HCl (1:4); H ₂ O (1:3)
146	B16	1	CH	6-CH ₃	6-NH ₂	H	HCl (1:5); H ₂ O (1:2)
147	B16	1	CH	6-CH ₃	5-NO ₂	H	HCl (1:4); H ₂ O (1:1)
148	B16	1	CH	6-CH ₃	5-NH ₂	H	HCl (1:5); H ₂ O (1:1)
149	B16	1	CH	6-CH ₃	7-CH ₃	H	
151	B16	1	CH	6-Cl	H	H	
153	B16	1	CH	6-Br	H	H	
154	B16	1	CH	6-OH	H	H	
155	B16	1	CH	6-OCH ₃	H	H	
156	B16	1	CH	4-Cl	H	H	HCl (1:4); H ₂ O (1:1)
157	B16	1	CH	4-OCH ₃	H	H	HCl (1:4); H ₂ O (1:2); 2-propanolate (1:1)
158	B16	1	CH	6-CH ₂ OCH ₃	H	H	HCl (1:4); H ₂ O (1:2)
159	B16	1	N	5-COOC ₂ H ₅	H	H	HCl (1:3); H ₂ O (1:1)
160	B16	1	CH	6-CH ₃	4-CH ₃	H	HCl (1:4); H ₂ O (1:2)
161	B16	1	CH	6-CH ₃	6-COOC ₂ H ₅	H	HCl (1:4); H ₂ O (1:1)

Co. No.	Ex. No.	n	a	R ^a	R ^b	R ^c	Physical data
162	B16	1	CH	6-CH ₃	6-CH ₂ OH	H	H ₂ O (1:1)
163	B16	1	CH	6-CH ₃	5-CF ₃	H	HCl (1:4); H ₂ O (1:2)
164	B16	1	CH	6-CH ₃	6-CF ₃	H	HCl (1:4); H ₂ O (1:1)
165	B16	1	CH	6-CON(CH ₃) ₂	H	H	HCl (1:3); H ₂ O (1:2)
166	B16	1	CH	6-CH ₃	5-Cl	H	HCl (1:4); H ₂ O (1:2)
22	B18	3	CH	H	H	H	HCl (1:4); H ₂ O (1:2)
167	B27a	1	CH	6-CH ₃	H	H	
305	B16	1	CH	6-CH ₃	5-CH ₃	H	-
306	B16	1	CH	6-CH ₃	6-Cl	H	HCl (1:4)

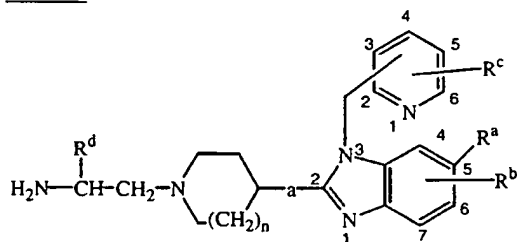
Table 6



Co. No.	Ex. No.	a	R ^a	R ^b	R ^c	R ^d	R ^e	Physical data
168	B27a	CH ₃ -OH		H	H	H	H	-
169	B1a	CH ₃ -[O-(CH ₂) ₂ -N(CH ₃) ₂]		6-CH ₃	H	H	H	HCl (1:5); H ₂ O (1:2)
152	B16	CH	H	H	H	CH ₃	H	HCl (1:4); H ₂ O (1:3)
170	B20	CH	3-NH ₂	H	H	H	CH(CH ₃) ₂	HCl (1:4); H ₂ O (1:3)
171	B20	N	5-CH ₃	H	H	H	CH ₃	mp. 175°C
172	B20	N	6-CH ₃	H	H	H	CH ₃	mp. 126°C
173	B20	N	3-CH ₃	5-CH ₃	6-CH ₃	H	CH ₃	HCl (1:4); H ₂ O (1:3); mp. 208°C
174	B20	N	3-CH ₃	5-CH ₃	6-CH ₃	H	CH(CH ₃) ₂	mp. 124°C
175	B16	N	H	H	H	CH ₃	H	HCl (1:3)
176	B16	N	3-CH ₃	5-CH ₃	6-CH ₃	H	H	HCl (1:4); H ₂ O (1:1); 2-propanolate (1:1)
177	B16	N	H	H	H	ethyl	H	HCl (1:3); H ₂ O (1:1)
178	B16	N	6-CH ₃	H	H	CH ₃	H	HCl (1:3); H ₂ O (1:1)
179	B16	CH	4-CH ₃	6-CH ₃	H	H	H	HCl (1:4); H ₂ O (1:2)
180	B16	CH	6-Cl	H	H	CH ₃	H	HCl (1:3); H ₂ O (1:1)
181	B16	CH	3-OH	6-CH ₃	H	H	H	HCl (1:3); H ₂ O (1:2)

Co. No.	Ex. No.	a	R ^a	R ^b	R ^c	R ^d	R ^e	Physical data
182	B16	CH	3-OCH ₃	6-CH ₃	H	H	H	
183	B16	CH	6-CH ₂ OH	H	H	CH ₃	H	HCl (1:4); H ₂ O (1:1)
184	B16	CH	3-[O-(CH ₂) ₂ -OC ₂ H ₅]	6-CH ₃	H	H	H	HCl (1:4); H ₂ O (1:2)
185	B16	CH	3-OCH ₂ CH ₂ Cl	6-CH ₃	H	H	H	HCl (1:3); H ₂ O (1:2)
186	B20	CH	H	H	H	CH ₃	CH ₃	HCl (1:3); H ₂ O (1:3); mp. 170°C
187	B20	N	6-CH ₃	H	H	H	CH(CH ₃) ₂	HCl (1:3); H ₂ O(1:3); mp. 200°C
188	B20	CH	H	H	H	CH ₃	CH(CH ₃) ₂	mp. 233°C
189	B20	N	5-CH ₃	H	H	H	CH(CH ₃) ₂	mp. 114°C
190	B20	CH	H	H	H	H	CH(CH ₃) ₂	mp. 50°C
25	B21	CH	3-Cl	5-CF ₃	H	H	H	
26	B22a	CH	3-OH	6-CH ₃	H	H	CH(CH ₃) ₂	
27	B23	CH	3-O-(CH ₂) ₂ -OH	6-CH ₃	H	H	H	HCl (1:3); H ₂ O(1:1)
28	B24	CH	4-CH ₂ OH	3-OH	5-CH ₂ OH	H	H	HCl (1:1)
192	B27a	CH	6-CH ₃	H	H	CH ₃	H	
299	B16	CH	3-CN	H	H	H	H	mp. 142°C
300	B20	CH	4-OCH ₃	3-OCH ₃	H	H	CH(CH ₃) ₂	HCl (1:4); H ₂ O(1:2); mp. 210°C
301	B16	CH	3-NH-SO ₂ -phenyl	6-Cl	H	H	H	mp. 161°C
307	B20	CH	5-OCH ₃	6-OCH ₃	H	H	CH(CH ₃) ₂	C ₂ H ₂ O ₄ (2:7); mp. 90°C

Table 7

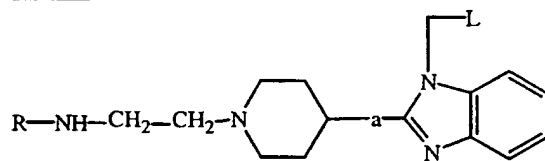


Co. No.	Ex. No.	n	*	a	R ^a	R ^b	R ^c	R ^d	Physical data
193	B16	2	2	CH ₂	H	H	H	H	ethanedioate (1:3); H ₂ O (1:2); mp. 125°C
194	B22b	1	2	NH	Cl	H	6-CH ₃	CH(CH ₃) ₂	
195	B22b	1	2	NH	H	7-CH ₃	6-CH ₃	CH(CH ₃) ₂	
196	B16	2	2	NH	H	H	H	H	ethanedioate (2:7); H ₂ O (1:2); mp. 170°C

Co. No.	Ex. No.	n	*	a	R ^a	R ^b	R ^c	R ^d	Physical data
197	B16	1	2	N(CH ₃)	H	H	H	H	
198	B16	1	2	N(CH ₂ -phenyl)	H	H	H	H	HCl (1:3); H ₂ O (1:1)
199	B27a	0	2	NH	H	H	H	H	HCl (1:4); H ₂ O (1:2)
200	B1a	1	2	CH ₂	OCH ₃	6-OCH ₃	H	H	HCl (1:4); H ₂ O (1:1); 2-propanolate (1:1)
201	B1a	1	3	NH	H	H	6-Br	H	HBr (1:4); H ₂ O (1:4)
202	B16	1	4	NH	H	H	H	H	HCl (1:4); H ₂ O (1:3)
296	B22b	1	2	NH	CH ₃	H	6-CH ₃	CH(CH ₃) ₂	-

* = position pyridyl

Table 8

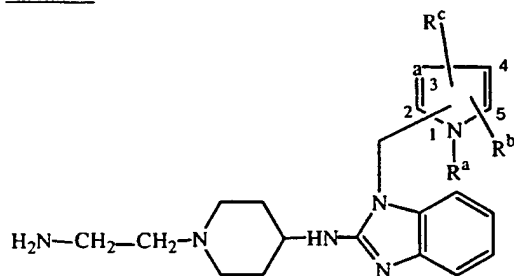


Co. No.	Ex. No.	L	a	R	Physical data
203	B16	4-pyrimidinyl	NH	H	HCl (1:4); H ₂ O (1:2)
204	B16	2-pyrimidinyl	NH	H	HCl (1:3); H ₂ O (1:1)
205	B16	2-pyrimidinyl	NH	H	
206	B16	3-pyridazinyl	NH	H	HCl (1:3); H ₂ O (1:1)
207	B16	4,6-dimethoxy-2-pyrimidinyl	NH	H	HCl (1:4); H ₂ O (1:3)
208	B16	2-pyrimidinyl	NH	H	HCl (1:4); H ₂ O (1:1)
209	B16	6-methyl-2-pyridyl	CH[N(CH ₃) ₂]	H	HCl (1:4); H ₂ O (1:2); 2-propanolate (1:1)
210	B7	6-methyl-2-pyridyl	CH[N(CH ₃) ₂]	-COOC(CH ₃) ₃	
211	B25a	2-pyridyl	NH	CH ₃	HCl (1:4); H ₂ O (1:2); mp. 224°C
212	B27a	2-[C(CH ₃) ₃]-6-OH-4-pyrimidinyl	NH	H	
320	B30	2-pyridinyl	NH	H	HCl (1:4); H ₂ O (1:1)
319	B27a	2,4-dimethyl-5-oxazolyl	NH	H	
329	B16	2,5-dimethyl-4-oxazolyl	NH	H	HCl (1:3); H ₂ O (1:1)
333	B16	5-methyl-3-isoxazolyl	NH	H	HCl (1:3); H ₂ O (1:1)
317	B27a	2-methyl-5-oxazolyl	NH	H	mp. 115°C; H ₂ O (1:1)
323	B27a	4-thiazolyl	NH	H	
326	B16	5-phenyl-1,2,4-oxadiazol-3-yl	NH	H	HCl (1:3)

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Co. No.	Ex. No.	L	a	R	Physical data
332	B16	2-(hydroxymethyl)-5-oxazolyl	NH	H	HCl (1:4); H ₂ O (1:2)
331	B16	3-methyl-5-isoxazolyl	NH	H	HCl (1:3); H ₂ O (1:1)
324	B16	2-(dimethylamino)-4-thiazolyl	CH ₂	H	HCl (1:4); H ₂ O (1:1); propanolate (1:1)
325	B27a	2-methyl-4-thiazolyl	CH ₂	H	
318	B27a	2-methyl-3-furanyl	NH	H	mp. 142°C
312	B25b	2-pyridinyl	NH	CH ₂ -CH ₂ OH	mp. 151°C
316	B30	2-methyl-5-oxazolyl	NH	H	HCl (1:4); H ₂ O (1:1)

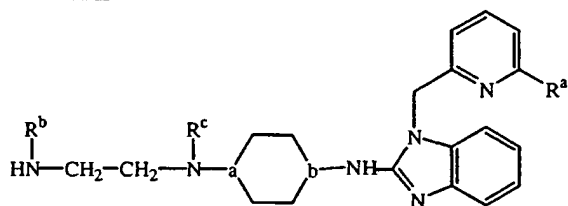
Table 9



Co. No.	Ex. No.	*	a	R ^a	R ^b	R ^c	Physical data
213	B16	2	N	CH ₂ C ₆ H ₅	H	H	HCl (1:4)
214	B16	5	N	H	4-CH ₃	H	HCl (1:4); H ₂ O (1:3)
215	B16	5	N	CH ₃	4-CH ₃	H	HCl (1:4); H ₂ O (1:2)
216	B16	2	N	CH ₃	5-COOC ₂ H ₅	4-CH ₃	HCl (1:4)
217	B16	2	N	CH ₃	5-Cl	H	HCl (1:4); H ₂ O (1:2)
218	B16	5	N	2-propyl	2-SCH ₃	H	HCl (1:4); H ₂ O (1:1)
219	B16	5	N	C ₂ H ₅	2-CH ₃	4-CH ₃	HCl (1:4); H ₂ O (1:2); 2-propanolate (1:1)
220	B16	5	N	CH ₃	2-CH ₃	4-CH ₃	HCl (1:4); H ₂ O (1:2)
21	B17	2	CH	CH ₃	5-CH ₃	H	H ₂ O (1:1)
221	B27a	2	CH	CH ₃	5-COOC ₂ H ₅	H	
222	B27a	2	CH	CH ₃	5-COOC ₂ H ₅	4-Br	

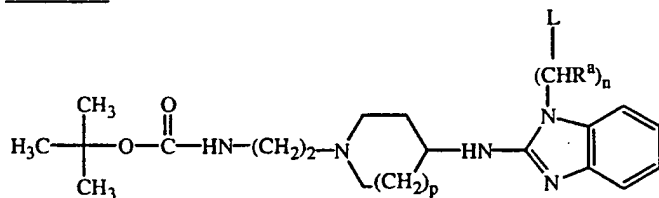
* position monocyclic heterocycle

Table 10



Co. No.	Ex. No.	a	b	R ^a	R ^b	R ^c	Physical data
14	B11	CH	CH	H	COCH ₃	H	(cis); mp. 126
15	B11	CH	CH	H	COCH ₃	H	(trans); mp. 200
223	B16	CH	CH	H	H	H	(trans); HCl (1:4); H ₂ O (1:1); mp. 210
29	B25a	CH	N	CH ₃	H	H	
224	B25a	CH	N	CH ₃	H	CH ₃	HCl (1:5); H ₂ O (1:3)

Table 11

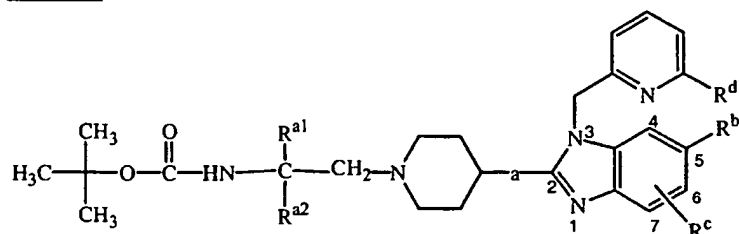


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Co. No.	Ex. No.	n	p	R ^a	L	Physical data
225	B7	1	1	H	6-chloro-2-pyridyl	
8	B7	1	1	H	6-methyl-2-pyrazinyl	
226	B7	1	2	H	2-pyridyl	
227	B7	1	1	H	5-methyl-2-pyrazinyl	
228	B7	1	1	CH ₃	2-pyridyl	
229	B7	1	2	H	2-pyridyl	
230	B7	1	1	H	4-methyl-1H-imidazol-5-yl	
231	B7	1	1	H	3-methyl-2-pyrazinyl	
232	B7	2	1	H	2-pyridyl	
233	B7	1	1	H	1,4-dimethyl-1H-imidazol-5-yl	
234	B7	1	1	H	4-pyrimidinyl	
235	B7	0	1	-	2-pyrimidinyl	
236	B7	1	1	H	6-(hydroxymethyl)-2-pyridyl	
237	B7	1	1	H	1,4-dimethyl-5-(-COOC ₂ H ₅)- 1H-imidazol-2-yl	

Co. No.	Ex. No.	n	p	R ^a	L	Physical data
238	B7	1	1	CH ₃	2-pyrazinyl	H ₂ O (1:1)
239	B7	1	1	H	3,5,6-trimethyl-2-pyrazinyl	
240	B7	1	1	Ethyl	2-pyrazinyl	
241	B7	1	1	CH ₃	6-methyl-2-pyrazinyl	
242	B7	1	1	H	5-chloro-1-methyl-1 <i>H</i> -imidazol-2-yl	
243	B7	1	1	H	4,6-dimethyl-2-pyridyl	
244	B7	1	1	H	6-bromo-2-pyridyl	
245	B7	1	1	H	6-(-COOC ₂ H ₅)-2-pyridyl	
246	B7	1	1	H	1,5-dimethyl-2-pyrrolyl	
247	B7	1	1	H	6-methoxy-2-pyridyl	
248	B7	1	1	H	4-chloro-2-pyridyl	
249	B7	1	1	H	4-methoxy-2-pyridyl	
250	B7	1	1	H	2-pyrimidinyl	
251	B7	1	1	H	3-methoxy-6-methyl-2-pyridyl	
252	B7	1	1	H	6-methyl-3-(-O-C ₂ H ₄ -O-C ₂ H ₅)-2-pyridyl	
253	B7	1	1	CH ₃	6-hydroxymethyl-2-pyridyl	
254	B7	1	1	H	6-bromo-3-pyridyl	
9	B8	1	1	H	2-(1,1-dimethylethyl)-6-hydroxy-4-pyrimidinyl	
255	B8	1	1	H	1-(phenylmethyl)-1 <i>H</i> -imidazol-2-yl	
256	B8	1	1	H	1-(2-propyl)-2-(-S-CH ₃)-1 <i>H</i> -imidazol-5-yl	
257	B8	1	1	CH ₃	6-chloro-2-pyridyl	
258	B8	1	1	H	1-ethyl-2,4-dimethyl-1 <i>H</i> -imidazol-5-yl	
259	B8	1	1	H	3-hydroxy-6-methyl-2-pyridyl	
260	B8	1	1	H	4,6-dimethoxy-2-pyrimidinyl	
261	B8	1	1	H	5-(-COOC ₂ H ₅)-2-pyrazinyl	
262	B8	1	1	H	1,2,4-trimethyl-1 <i>H</i> -imidazol-5-yl	
10	B9a	1	1	H	3-(-O-C ₂ H ₄ Cl)-6-methyl-2-pyridyl	
263	B9a	1	1	H	6-(-CH ₂ -O-CH ₃)-2-pyridyl	
11	B9b	1	1	H	3-[-O-C ₂ H ₄ -N(CH ₃) ₂]-6-methyl-2-pyridyl	
12	B10a	1	1	H	6-chloro-3-pyridazinyl	
13	B10b	1	1	H	3-pyridazinyl	
330	B7	1	1	H	2-methyl-4-methoxycarbonyl-5-oxazolyl	

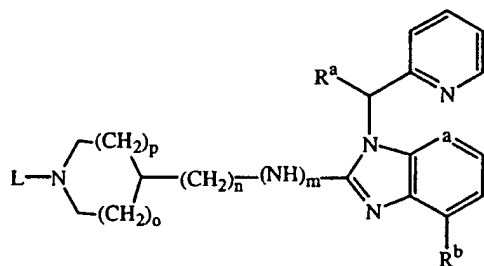
Table 12



Co. No.	Ex. No.	R ^{a1} , R ^{a2}	R ^b	R ^c	a	R ^d	Physical data
264	B7	H, H	OCH ₃	6-OCH ₃	CH ₂	H	H ₂ O (1:1)
265	B7	H, H	H	H	N(CH ₃)	H	
266	B7	H, H	H	H	N(CH ₂ -C ₆ H ₅)	H	
267	B7	H, H	Cl	6-Cl	NH	CH ₃	
268	B7	H, H	CH ₃	6-CH ₃	NH	CH ₃	
269	B7	H, H	H	4-Cl	NH	CH ₃	
270	B7	H, H	H	7-Cl	NH	CH ₃	
271	B7	H, H	H	6-NO ₂	NH	CH ₃	
272	B7	H, H	NO ₂	H	NH	CH ₃	
273	B7	H, H	H	7-CH ₃	NH	CH ₃	
274	B7	H, H	H	4-CH ₃	NH	CH ₃	
275	B7	H, H	H	6-ethoxy-carbonyl	NH	CH ₃	
276	B7	H, H	H	6-hydroxy-methyl	NH	CH ₃	
277	B7	H, H	CF ₃	H	NH	CH ₃	
278	B7	H, H	H	6-CF ₃	NH	CH ₃	
279	B7	H, H	H	H	NH	-CO-N(CH ₃) ₂	
280	B7	H, H	Cl	H	NH	CH ₃	
16	B12	CH ₃ , CH ₃	H	H	NH	H	
17	B13	H, H	-NH ₂	H	NH	CH ₃	
281	B13	H, H	H	6-NH ₂	NH	CH ₃	
19	B15	-CH ₂ OH, H	H	H	NH	H	

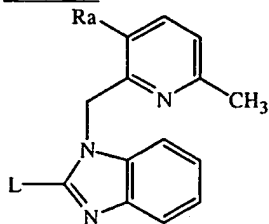
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Table 13



Co. No.	Ex. No.	n	m	o	p	a	R ^a	R ^b	L	Physical data
6	B5	1	0	2	1	CH	H	H	H	
283	B27a	1	0	1	1	N	H	H	-(CH ₂) ₂ -NH ₂	HCl (1:4), H ₂ O (1:1); 2-propanolate (1:1)
284	B27a	1	1	1	1	N	H	H	-(CH ₂) ₂ -NH ₂	HCl (1:1)
285	B27a	1	1	0	2	CH	H	H	-(CH ₂) ₂ -NH ₂	HCl (1:4), H ₂ O (1:1); mp. 205°C
286	B4	1	1	0	2	CH	H	H	H	
30	B26	0	1	1	1	CH	CH ₃	H	-CH(CH ₃)-CH ₂ -NH ₂	mp. 85°C

Table 14



5

Co. No.	Ex. No.	R _a	L	Physical data
288	B25a	H		
289	B4	H		
309	B19	H	-NH-(CH ₂) ₃ -NH ₂	HCl (1:3); H ₂ O (1:2)
347	B16	H	-NH-CH(CH ₃)-(CH ₂) ₂ -NH-(CH ₂) ₂ -NH ₂	HCl(1:4); 2-propanolate (1:1)
345	B19	H	-N(CH ₃)-(CH ₂) ₃ -NH-(CH ₂) ₂ -NH ₂	HCl (1:4); H ₂ O (1:1)
346	B19	H		HCl (1:4); H ₂ O (1:1)

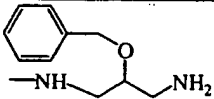
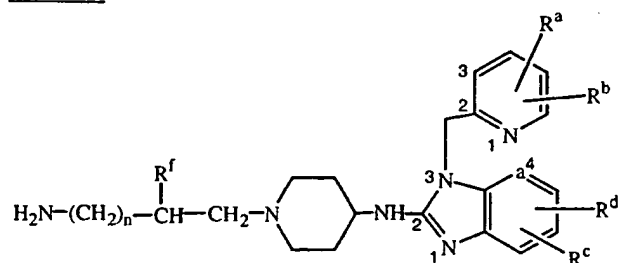
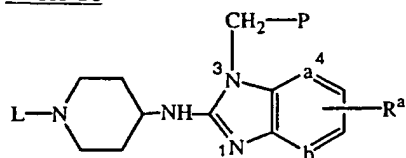
Co. No.	Ex. No.	R _a	L	Physical data
341	B25a	H		HCl (1:3); H ₂ O (1:1)
313	B25c	OH	-NHCH ₂ CH(OH)CH ₂ NH ₂	

Table 15



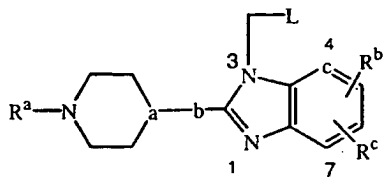
Co. No.	Ex. No.	a	n	R ^a	R ^b	R ^c	R ^d	R ^f	Physical data
290	B16	CH	0	3-OH	6-CH ₃	7-CH ₃	H	H	HCl (1:4); H ₂ O (1:4)
291	B22b	N	0	3-OH	6-CH ₃	7-CH ₃	H	CH-(CH ₃) ₂	-
292	B22b	CH	0	3-OH	6-CH ₃	7-CH ₃	H	CH ₃	HCl (1:4); H ₂ O (1:3)
293	B22b	CH	0	3-OH	6-CH ₃	7-CH ₃	H	CH-(CH ₃) ₂	-
195	B22b	CH	0	6-CH ₃	H	7-CH ₃	H	CH-(CH ₃) ₂	-
303	B28	CH	1	6-CH ₃	H	7-CH ₃	H	OH	H ₂ O (1:1)
304	B22b	CH	0	6-CH ₃	H	6-CH ₃	H	CH-(CH ₃) ₂	-
342	B16	CH	0	3-OH	6-CH ₃	5-Cl	7-CH ₃	H	HCl (1:4), 2-propanolate (1:1)
348	B16	CH	0	3-OH	6-CH ₃	5-Br	7-CH ₃	H	HCl (1:4)
351	B22b	CH	0	3-OH	6-CH ₃	4-CH ₃	H	CH-(CH ₃) ₂	HCl (1:4); H ₂ O (1:1)
340	B16	CH	0	3-OH	6-CH ₃	4-CH ₃	H	H	HCl (1:4); H ₂ O (1:2)
344	B16	CH	0	3-OH	6-CH ₃	4-CH ₃	6-Cl	H	HCl (1:4); H ₂ O (1:4)
349	B16	CH	0	3-OH	6-CH ₃	5-(4-fluoro-benzoyl)	H	H	HCl (1:4); H ₂ O (1:2)
350	B16	CH	0	3-OH	6-CH ₃	6-(4-fluoro-benzoyl)	H	H	HCl (1:4); H ₂ O (1:2)
355	B16	CH	0	3-OH	6-CH ₃	7-CH ₃	H	H	
356	B16	CH	0	3-OH	6-CH ₃	7-CH ₃	H	H	C ₄ H ₆ O ₄ (1:1); H ₂ O(1:1)
357	B16	CH	0	3-OH	6-CH ₃	7-CH ₃	H	H	C ₄ H ₆ O ₅ (1:1); H ₂ O(1:2)
353	B16	CH	0	3-OH	6-CH ₃	7-CH ₃	H	H	HCl(1:4); H ₂ O(1:5)

Table 16



Co. No.	Ex. No.	a	b	R ^a	L	P	Physical data
295	B22b	CH	CH	5-Cl	-CH ₂ -CH(NH ₂)-CH(CH ₃) ₂		H ₂ O (1:1)
297	B22b	CH	CH	5-Cl	-CH ₂ -CH(NH ₂)-CH(CH ₃) ₂		
298	B22b	CH	CH	H	-CH ₂ -CH(NH ₂)-CH(CH ₃) ₂		
310	B1b	CH	N	H	H		HBr (1:3).H ₂ O (1:1).C ₂ H ₆ O (1:1)
302	B1a	CH	CH	5-Cl	H		
321	B27a	N	CH	H	-CH ₂ -CH ₂ -NH ₂	2,4-dimethyl-5-oxazolyl	
339	B8	N	CH	7-CH ₃	-C(=O)-O-CH ₂ -CH ₃		mp. 171°C
336	B9b	CH	CH	H	-C(=O)-O-C(CH ₃) ₃		
337	B25a	CH	CH	H	-C(=O)-O-CH ₂ -CH ₃		
352	B7	CH	CH	7-CH ₃	-(CH ₂) ₃ -NH-C(=O)OC(CH ₃) ₃		.HCl(1:4)
354	B16	CH	CH	7-CH ₃	-(CH ₂) ₃ -NH-CH=O		

Table 17



Co. No.	Ex. No.	a	b	c	R ^a	R ^b	R ^c	L	Physical data
343	B1b	CH	NH	CH	H	5-Br	7-CH ₃	3-hydroxy-6-methyl-2-pyridinyl	HBr (1:3)
338	B1b	CH	NH	CH	H	H	7-CH ₃	3-hydroxy-6-methyl-2-pyridinyl	
335	B20	N	NH	CH	$\text{—CH}_2\text{—CH—NH}_2$ CH(CH ₃) ₂	H	H	2-pyridinyl	mp. 198°C
334	B27a	N	NH	CH	—(CH ₂) ₂ —NH ₂	H	H	2-pyridinyl	mp. 186
322	B27a	N	CH ₂	N	—(CH ₂) ₂ —NH ₂	H	H	2-methyl-5-oxazolyl	
314	B27b	CH	CH ₂	N	—(CH ₂) ₂ —NH ₂	H	H	5-methoxymethyl-2-furanyl	

5 C. Pharmacological example

Example C1 : In vitro screening for activity against Respiratory Syncytial Virus.

The percent protection against cytopathology caused by viruses (antiviral activity or IC₅₀) achieved by tested compounds and their cytotoxicity (CC₅₀) were both calculated from dose-response curves. The selectivity of the antiviral effect is represented by the selectivity index (SI), calculated by dividing the CC₅₀ (cytotoxic dose for 50% of the cells) by the IC₅₀ (antiviral activity for 50 % of the cells).

Automated tetrazolium-based colorimetric assays were used for determination of IC₅₀ and CC₅₀ of test compounds. Flat-bottom, 96-well plastic microtiter trays were filled with 180 µl of Eagle's Basal Medium, supplemented with 5 % FCS (0% for FLU) and 20 mM Hepes buffer. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 µl volumes to a series of triplicate wells so as to allow simultaneous evaluation of their effects on virus- and mock-infected cells. Five five-fold dilutions were made directly in the microtiter trays using a robot system. Untreated virus controls, and HeLa cell controls were included in each test. Approximately 100 TCID₅₀ of Respiratory Syncytial Virus was added to two of the three rows in a volume of 50 µl. The same volume of medium was added to the third row to measure the cytotoxicity of the compounds at the same concentrations as those used to measure the antiviral activity. After two hours of incubation, a suspension (4 x 10⁵ cells/ml) of HeLa

cells was added to all wells in a volume of 50 μ l. The cultures were incubated at 37°C in a 5% CO₂ atmosphere. Seven days after infection the cytotoxicity and the antiviral activity was examined spectrophotometrically. To each well of the microtiter tray, 25 μ l of a solution of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added. The trays were further incubated at 37°C for 2 hours, after which the medium was removed from each cup. Solubilization of the formazan crystals was achieved by adding 100 μ l 2-propanol. Complete dissolution of the formazan crystals were obtained after the trays have been placed on a plate shaker for 10 min. Finally, the absorbances were read in an eight-channel computer-controlled photometer (Multiskan MCC, Flow Laboratories) at two wavelengths (540 and 690 nm). The absorbance measured at 690 nm was automatically subtracted from the absorbance at 540 nm, so as to eliminate the effects of non-specific absorption.

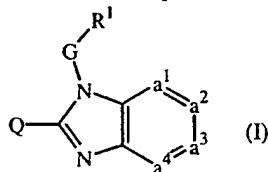
Particular IC₅₀, CC₅₀ and SI values are listed in Table 18 hereinbelow.

15 Table 18

Co. No.	IC ₅₀ (μ M)	CC ₅₀ (μ M)	SI
290	0.00013	>0.010	>79
292	0.00032	63.85	199526
351	0.00063	50.04	79433
297	0.00251	>99.93	>39811
296	0.00631	19.95	3162
27	0.0126	>100.08	>7943
192	0.0631	63.1	1000
144	0.1259	50.11	398
222	0.5012	39.59	79
142	1.2589	40.28	32
145	2.5119	>50.24	>20

Claims

1. Use of a compound for the manufacture of a medicament for the treatment of viral infections, wherein the compound is a compound of formula



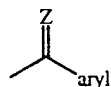
- 5 a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof, wherein

-a¹=a²-a³=a⁴- represents a bivalent radical of formula

- 10 -CH=CH-CH=CH- (a-1);
 -N=CH-CH=CH- (a-2);
 -CH=N-CH=CH- (a-3);
 -CH=CH-N=CH- (a-4); or
 -CH=CH-CH=N- (a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C₁₋₆alkyl, nitro, amino, hydroxy,

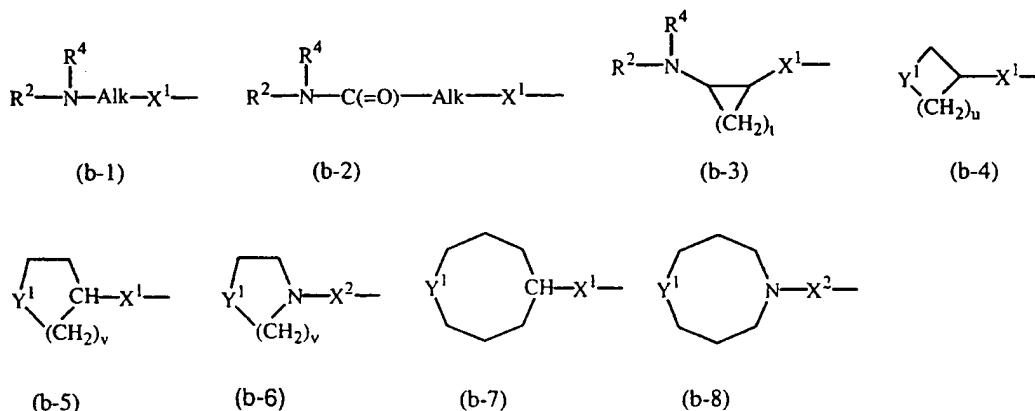
- 15 C₁₋₆alkyloxy, polyhaloC₁₋₆alkyl, carboxyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, hydroxyC₁₋₆alkyl, or a radical of formula



wherein =Z is =O, =CH-C(=O)-NR^{5a}R^{5b}, =CH₂, =CH-C₁₋₆alkyl, =N-OH or =N-O-C₁₋₆alkyl;

20

Q is a radical of formula



- 25 wherein Alk is C₁₋₆alkanediyl;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4 , S, $S(=O)$, $S(=O)_2$, O, CH_2 , $C(=O)$, $C(=CH_2)$, $CH(OH)$, $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2 ;

X^2 is a direct bond, CH_2 , $C(=O)$, NR^4 , $C_{1-4}alkyl-NR^4$, $NR^4-C_{1-4}alkyl$;

5 t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R^3 ; with the proviso that when R^3 is hydroxy or $C_{1-6}alkyloxy$, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or $C_{1-10}alkanediyl$;

R^1 is a monocyclic heterocycle selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, and isothiazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, $C_{1-6}alkyl$, $C_{1-6}alkyloxy$, $C_{1-6}alkylthio$, $C_{1-6}alkyloxyC_{1-6}alkyl$, aryl, aryl $C_{1-6}alkyl$, aryl $C_{1-6}alkyloxy$, hydroxy $C_{1-6}alkyl$, mono-or di($C_{1-6}alkyl$)amino, mono-or di($C_{1-6}alkyl$)amino $C_{1-6}alkyl$, polyhalo $C_{1-6}alkyl$, $C_{1-6}alkylcarbonylamino$, $C_{1-6}alkyl-SO_2-NR^{5c}$ -, aryl- SO_2-NR^{5c} -, $C_{1-6}alkyloxy$ carbonyl, $-C(=O)-NR^{5c}R^{5d}$, $HO(-CH_2-CH_2-O)_n$ -, halo $(-CH_2-CH_2-O)_n$ -, $C_{1-6}alkyloxy(-CH_2-CH_2-O)_n$ -, aryl $C_{1-6}alkyloxy(-CH_2-CH_2-O)_n$ - and mono-or di($C_{1-6}alkyl$)amino $(-CH_2-CH_2-O)_n$ -;

each n independently is 1, 2, 3 or 4;

25 R^2 is hydrogen, formyl, $C_{1-6}alkylcarbonyl$, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, $C_{3-7}cycloalkyl$ substituted with $N(R^6)_2$, or $C_{1-10}alkyl$ substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, $C_{3-7}cycloalkyl$, $C_{2-5}alkanediyl$, piperidinyl, mono-or di($C_{1-6}alkyl$)amino, $C_{1-6}alkyloxy$ carbonylamino, aryl and aryloxy;

30 R^3 is hydrogen, hydroxy, $C_{1-6}alkyl$, $C_{1-6}alkyloxy$, aryl $C_{1-6}alkyl$ or aryl $C_{1-6}alkyloxy$;

R^4 is hydrogen, $C_{1-6}alkyl$ or aryl $C_{1-6}alkyl$;

R^{5a} , R^{5b} , R^{5c} and R^{5d} each independently are hydrogen or $C_{1-6}alkyl$; or

R^{5a} and R^{5b} , or R^{5c} and R^{5d} taken together form a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;

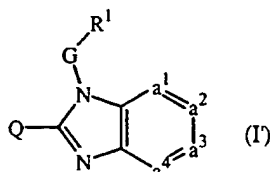
35 R^6 is hydrogen, $C_{1-4}alkyl$, formyl, hydroxy $C_{1-6}alkyl$, $C_{1-6}alkylcarbonyl$ or $C_{1-6}alkyloxy$ carbonyl;

aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, polyhaloC₁₋₆alkyl, and C₁₋₆alkyloxy;

Het is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl.

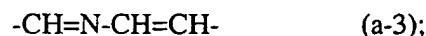
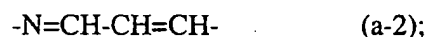
5

2. A compound of formula (I')



a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof, wherein

10 -a¹=a²-a³=a⁴- represents a radical of formula

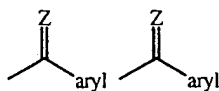


15 -CH=CH-CH=N- (a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C₁₋₆alkyl, nitro, amino, hydroxy,

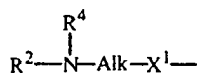
C₁₋₆alkyloxy, polyhaloC₁₋₆alkyl, carboxyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, hydroxyC₁₋₆alkyl, or a

20 radical of formula

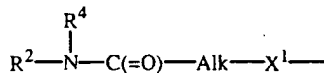


wherein =Z is =O, =CH-C(=O)-NR^{5a}R^{5b}, =CH₂, =CH-C₁₋₆alkyl, =N-OH or =N-O-C₁₋₆alkyl;

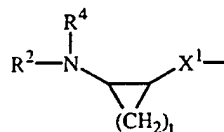
Q is a radical of formula



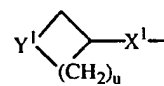
(b-1)



(b-2)



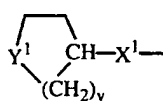
(b-3)



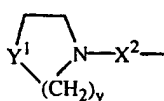
(b-4)

25

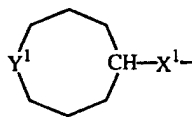
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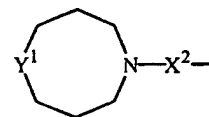
(b-5)



(b-6)



(b-7)



(b-8)

wherein Alk is C₁₋₆alkanediyl;

Y¹ is a bivalent radical of formula -NR²- or -CH(NR²R⁴)-;

X¹ is NR⁴, S, S(=O), S(=O)₂, O, CH₂, C(=O), C(=CH₂), CH(OH), CH(CH₃),
 5 CH(OCH₃), CH(SCH₃), CH(NR^{5a}R^{5b}), CH₂-NR⁴ or NR⁴-CH₂;

X² is a direct bond, CH₂, C(=O), NR⁴, C₁₋₄alkyl-NR⁴, NR⁴-C₁₋₄alkyl;

t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

- 10 whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R³; with the proviso that when R³ is hydroxy or C₁₋₆alkyloxy, then R³ can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C₁₋₁₀alkanediyl;

- 15 R¹ is a monocyclic heterocycle selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, imidazolyl and pyrazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, aryl, arylC₁₋₆alkyl, arylC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono-or
 20 di(C₁₋₆alkyl)amino, mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkyl-carbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, aryl-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, arylC₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n;

each n independently is 1, 2, 3 or 4;

- 25 R² is hydrogen, formyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C₃₋₇cycloalkyl substituted with N(R⁶)₂, or C₁₋₁₀alkyl substituted with N(R⁶)₂ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C₃₋₇cycloalkyl, C₂₋₅alkanediyl, piperidinyl, mono-or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonylamino, aryl and aryloxy;

- 30 R³ is hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, arylC₁₋₆alkyl or arylC₁₋₆alkyloxy;

R⁴ is hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl;

R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C₁₋₆alkyl; or

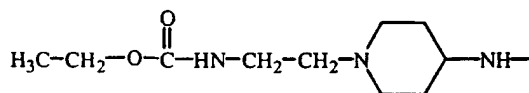
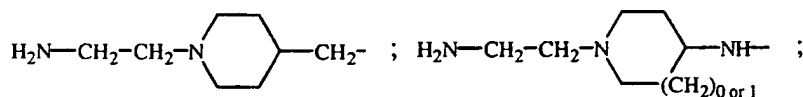
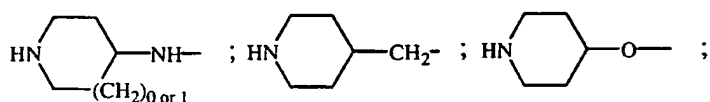
R^{5a} and R^{5b} , or R^{5c} and R^{5d} taken together form a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;

R^6 is hydrogen, C_{1-6} alkyl, formyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyl or C_{1-6} alkyloxycarbonyl;

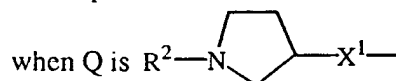
- 5 aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, polyhalo C_{1-6} alkyl, and C_{1-6} alkyloxy;

provided that when G is methylene, and R^1 is 2-pyridyl, 3-pyridyl, 6-methyl-2-pyridyl, 2-pyrazinyl or 5-methyl-imidazol-4-yl, and $-a^1=a^2-a^3=a^4-$ is $-CH=CH-CH=CH-$ or

- 10 $-N=CH-CH=CH-$, then Q is other than

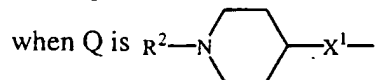


3. A compound as claimed in claim 2 wherein the following restrictions apply :



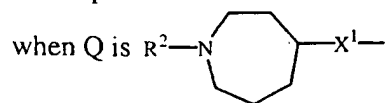
wherein X^1 is NR^4 , O, S, $S(=O)$, $S(=O)_2$, CH_2 , $C(=O)$, $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6} alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6} alkyl.

4. A compound as claimed in claim 2 wherein the following restrictions apply :



wherein X^1 is NR^4 , O, S, $S(=O)$, $S(=O)_2$, CH_2 , $C(=O)$, $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6} alkyl, pyridyl substituted with 1 or 2 C_{1-6} alkyloxy, pyrazinyl, pyrrolyl, pyrrolyl substituted with C_{1-6} alkyl, imidazolyl and imidazolyl substituted with C_{1-6} alkyl.

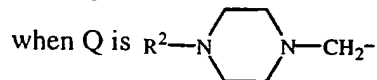
5. A compound as claimed in claim 2 wherein the following restrictions apply :



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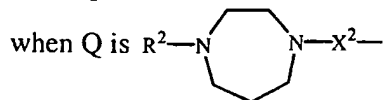
wherein X^1 is NR^4 , O, S, $S(=O)$, $S(=O)_2$, CH_2 , $C(=O)$, $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6} alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6} alkyl.

- 5 6. A compound as claimed in claim 2 wherein the following restrictions apply :



then R^1 is other than pyridyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6} alkyl.

- 10 7. A compound as claimed in claim 2 wherein the following restrictions apply :



wherein X^2 is CH_2 or a direct bond, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6} alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6} alkyl.

15

8. A compound as claimed in claim 2 wherein the compound is selected from
 (\pm)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-7-methyl-1*H*-
 benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride monohydrate;
 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-1*H*-benzimidazol-1-yl]methyl]-3-
 20 pyridinol; (\pm)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(1,4-
 dimethyl-1*H*-imidazol-5-yl)methyl]-1*H*-benzimidazol-2-amine monohydrate; (\pm)-
N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(6-methyl-2-
 pyridinyl)methyl]-1*H*-benzimidazol-2-amine; (\pm)-2-[[2-[(3-amino-2-
 hydroxypropyl)amino]-1*H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol; *N*-[1-
 25 (2-aminoethyl)-4-piperidinyl]-1-[[3-(2-ethoxyethoxy)-6-methyl-2-
 pyridinyl]methyl]-1*H*-benzimidazol-2-amine tetrahydrochloride dihydrate; (\pm)-*N*-
 [1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-chloro-1,4-dimethyl-1*H*-imidazol-
 5-yl)methyl]-1*H*-benzimidazol-2-amine; (\pm)-*N*-[1-(2-amino-3-methylbutyl)-4-
 piperidinyl]-6-chloro-1-[(2-chloro-1,4-dimethyl-1*H*-imidazol-5-yl)methyl]-1*H*-
 30 benzimidazol-2-amine; (\pm)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-methyl-
 1-[(6-methyl-2-pyridinyl)methyl]-1*H*-benzimidazol-2-amine; (\pm)-*N*-[1-(2-
 aminopropyl)-4-piperidinyl]-1-[(3,5,6-trimethylpyrazinyl)methyl]-1*H*-
 benzimidazol-2-amine tetrahydrochloride trihydrate; (\pm)-*N*-[1-(2-amino-3-
 methylbutyl)-4-piperidinyl]-1-[(3,5,6-trimethylpyrazinyl)methyl]-1*H*-
 35 benzimidazol-2-amine; *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[[3-(2-chloroethoxy)-

- 6-methyl-2-pyridinyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride dihydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[3-amino-2-pyridinyl)methyl]-*1H*-benzimidazol-2-amine tetrahydrochloride trihydrate; 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl)methyl]-6-methyl-3-pyridinol tetrahydrochloride; (±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-7-methyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]-6-methyl-3-pyridinol; 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-6-chloro-4-methyl-*1H*-benzimidazol-1-yl)methyl]-6-methyl-3-pyridinol tetrahydrochloride 2-propanolate (1:1); (±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl)methyl]-6-methyl-3-pyridinol; (±)-2-[[2-[[1-(2-aminopropyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl)methyl]-6-methyl-3-pyridinol tetrahydrochloride trihydrate; 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-7-methyl-*1H*-benzimidazol-1-yl)methyl]-6-methyl-3-pyridinol tetrahydrochloride dihydrate; 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-6-bromo-4-methyl-*1H*-benzimidazol-1-yl)methyl]-6-methyl-3-pyridinol tetrahydrochloride; 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl)methyl]-6-methyl-3-pyridinol tetrahydrochloride monohydrate; (±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl)methyl]-6-methyl-3-pyridinol; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-[(6-methyl-2-pyridinyl)methyl]-*1H*-benzimidazol-2-amine; a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex and stereochemically isomeric form thereof.
9. A compound selected from
- 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-5-chloro-7-methyl-*1H*-benzimidazol-1-yl)methyl]-6-methyl-3-pyridinol tetrahydrochloride tetrahydrate; *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2,4-dimethyl-5-oxazolyl)methyl]-*1H*-benzimidazol-2-amine; *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2,5-dimethyl-4-oxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate; 4-[[3-[[5-(methoxymethyl)-2-furanyl)methyl]-3*H*-imidazo[4,5-*b*]pyridine-2-yl)methyl]-1-piperidineetanamine; *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(5-methyl-3-isoxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate; *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-5-oxazolyl)methyl]-*1H*-benzimidazol-2-amine monohydrate; *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-5-oxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate; *N*-[1-(2-aminoethyl)-4-piperidinyl]-3-[(2,4-dimethyl-5-oxazolyl)methyl]-3*H*-imidazo[4,5-*b*]pyridin-2-amine; 4-[[3-[(2-methyl-5-

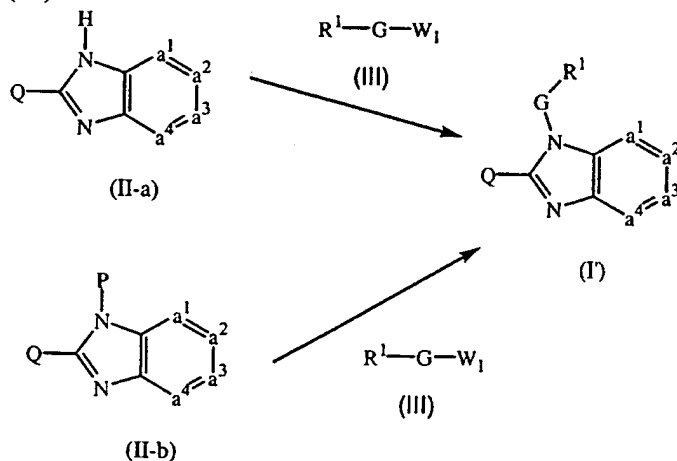
oxazolyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl)methyl]-1-piperazineethanamine; N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-thiazolylmethyl)-*1H*-benzimidazol-2-amine; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(5-phenyl-1,2,4-oxadiazol-3-yl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride; 5-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl)methyl]-2-oxazolemethanol tetrahydrochloride dihydrate; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(3-methyl-5-isoxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate; 4-[[1-[[2-(dimethylamino)-4-thiazolyl)methyl]-*1H*-benzimidazol-2-yl)methyl]-1-piperidineethanamine tetrahydrochloride monohydrate 2-propanolate (1:1); ethyl 5-[[2-[[1-[[2-[(1,1-dimethylethoxy)carbonyl]amino]ethyl]-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl)methyl]-2-methyl-4-oxazolecarboxylate; 4-[[1-[(2-methyl-4-thiazolyl)methyl]-*1H*-benzimidazol-2-yl)methyl]-1-piperidineethanamine; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-3-furanyl)methyl]-*1H*-benzimidazol-2-amine; ethyl 4-[[3-[(3-hydroxy-6-methyl-2-pyridinyl)methyl]-7-methyl-3H-imidazo[4,5-b]pyridine-2-yl]amino]-1-piperidinecarboxylate; 1,1-dimethylethyl 4-[[1-[[3-[2-(dimethylamino)ethoxy]-6-methyl-2-pyridinyl)methyl]-*1H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate; ethyl 4-[[1-[(3-amino-2-pyridinyl)methyl]-*1H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate; N-[1-(6-methyl-2-pyridinyl)-*1H*-benzimidazol-2-yl]-1-(3-pyridinylcarbonyl)-4-piperidinamine;

a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex and stereochemically isomeric form thereof.

10. A compound as claimed in anyone of claims 2 to 9 for use as a medicine.
11. Use of a compound as claimed in claim 9 for the manufacture of a medicament for the treatment of viral infections.
12. Use of a compound according to claim 1 or 11 wherein said viral infection is a respiratory syncytial virus infection.
13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in claim 2 or claim 9.
14. A process of preparing a composition as claimed in claim 13 characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as claimed in claim 2 or claim 9.

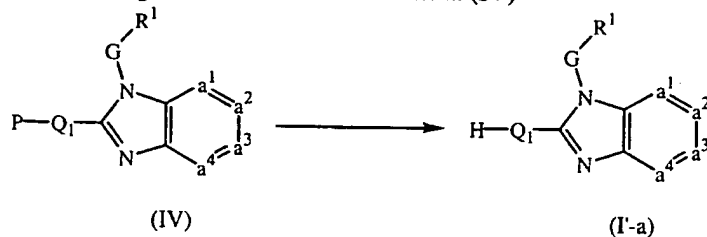
15. A process of preparing a compound as claimed in claim 2, characterized by

a) reacting an intermediate of formula (II-a) or (II-b) with an intermediate of formula (III)



with R^1 , G, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and W_1 being a suitable leaving group, in the presence of a suitable base and in a suitable reaction-inert solvent;

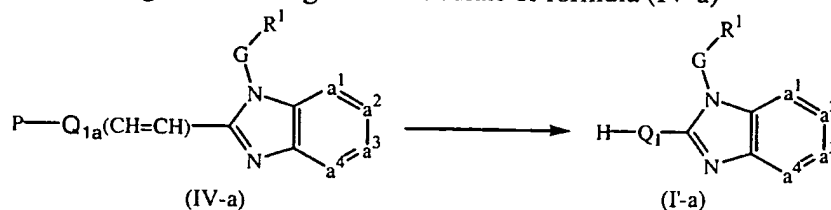
10 b) deprotecting an intermediate of formula (IV)



with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, $H-Q_1$ being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen, and P being a protective group;

15

c) deprotecting and reducing an intermediate of formula (IV-a)

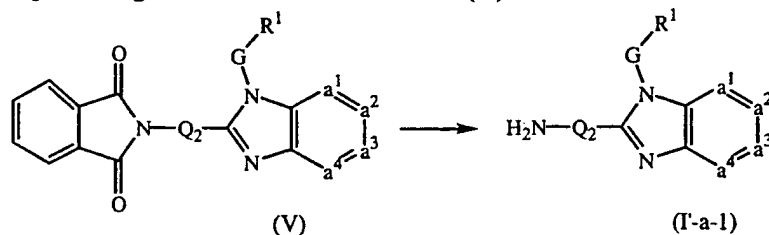


with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, $H-Q_1$ being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen,

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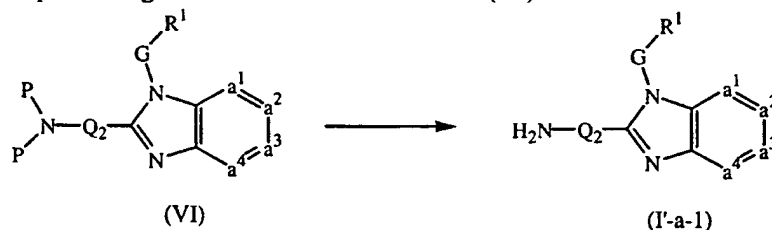
$Q_{1a}(CH=CH)$ being defined as Q_1 provided that Q_1 comprises an unsaturated bond, and P being a protective group

d) deprotecting an intermediate of formula (V)



5 with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H_2N-Q_2 being defined as Q according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen;

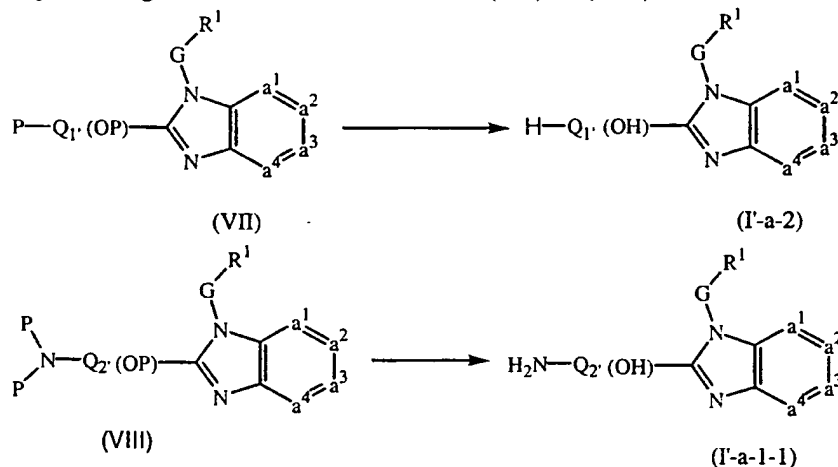
e) deprotecting an intermediate of formula (VI)



10

with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H_2N-Q_2 being defined as Q according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and P being a protective group;

15 f) deprotecting an intermediate of formula (VII) or (VIII)

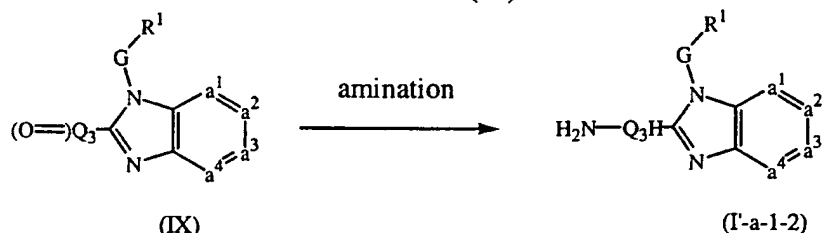


20 with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, $H-Q_1(OH)$ being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen and provided that Q comprises a hydroxy moiety, $H_2N-Q_2(OH)$ being defined as Q

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according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen and provided that Q comprises a hydroxy moiety, and P being a protective group;

g) amination of an intermediate of formula (IX)

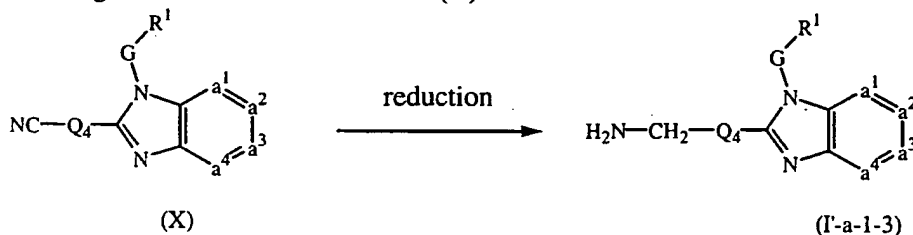


5

with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H_2N-Q_3H being defined as Q according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6 , or R^2 and R^4 substituents contains at least one hydrogen, in the presence of a suitable amination reagent;

10

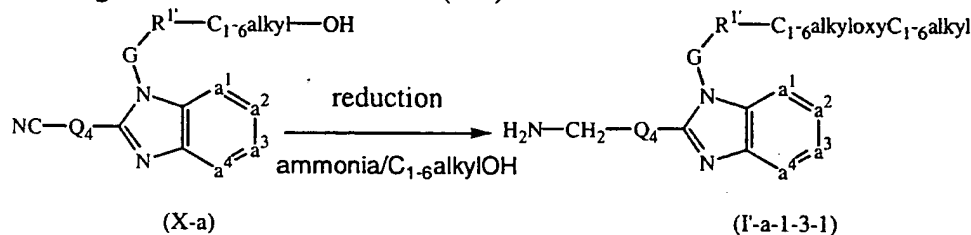
h) reducing an intermediate of formula (X)



15

with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $H_2N-CH_2-Q_4$ being defined as Q according to claim 2 provided that Q comprises a $-CH_2-NH_2$ moiety, in the presence of a suitable reducing agent;

i) reducing an intermediate of formula (X-a)

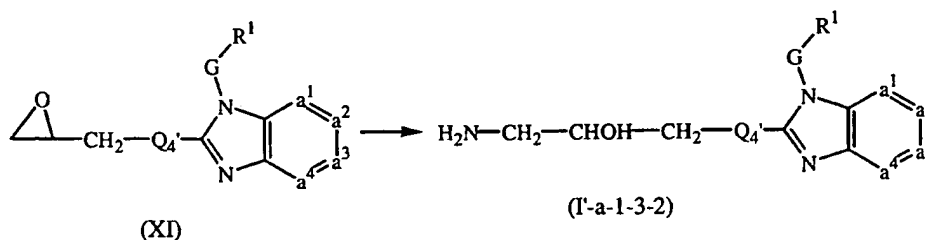


20

with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, $H_2N-CH_2-Q_4$ being defined as Q according to claim 2 provided that Q comprises a $-CH_2-NH_2$ moiety, and $R^{1'}$ being defined as R^1 according to claim 2 provided that it comprises at least one substituent, in the presence of a suitable reducing agent and suitable solvent;

25 j) amination of an intermediate of formula (XI)

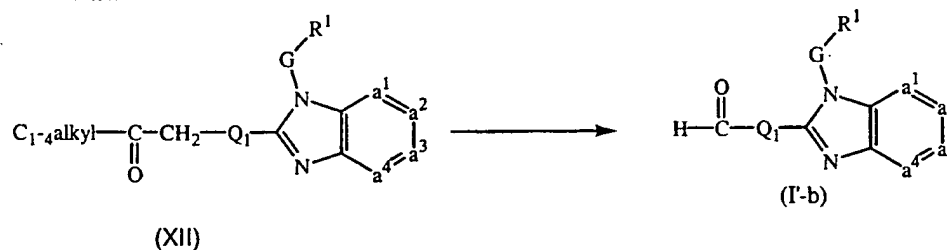
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with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $H_2N-CH_2-CHOH-CH_2-Q_4'$ being defined as Q according to claim 2 provided that Q comprises a $CH_2-CHOH-CH_2-NH_2$ moiety, in the presence of a suitable amination reagent;

5

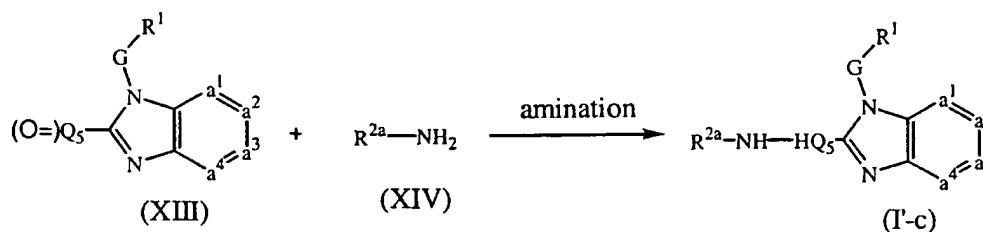
- k) reacting an intermediate of formula (XII) with formic acid, formamide and ammonia



with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $H-C(=O)-Q_1$ being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is formyl;

10

- l) amination of an intermediate of formula (XIII) by reaction with an intermediate of formula (XIV)



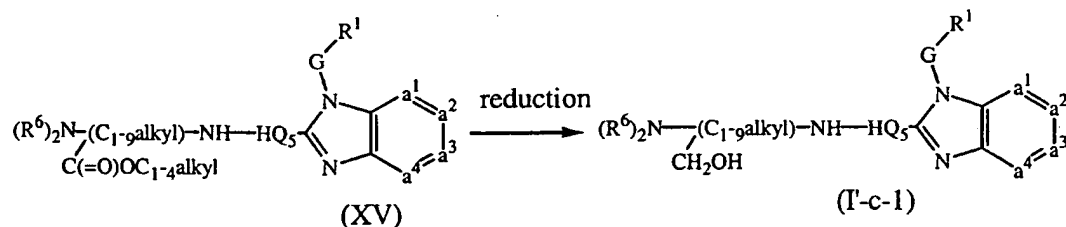
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with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $R^{2a}-NH-HQ_5$ being defined as Q according to claim 2 provided that R^2 is other than hydrogen and is represented by R^{2a} , R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, in the presence of a suitable reducing agent;

20

- m) reducing an intermediate of formula (XV)

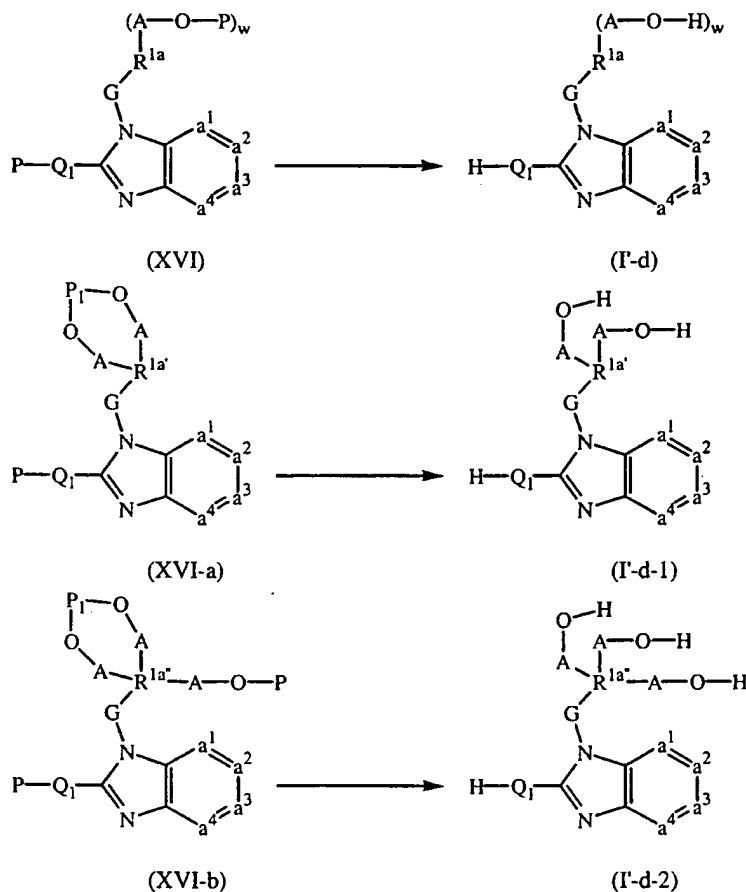
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with R^1 , G , and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and

$(R^6)_2N-[(C_{1-9}alkyl)CH_2OH]-NH-HQ_5$ being defined as Q according to claim 2 provided that R^2 is other than hydrogen and is represented by $C_{1-10}alkyl$ substituted with $N(R_6)_2$ and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, and provided that R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, with a suitable reducing agent;

10 n) deprotecting an intermediate of formula (XVI), (XVI-a) or (XVI-b)



with G , and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $H-Q_1$ being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen,

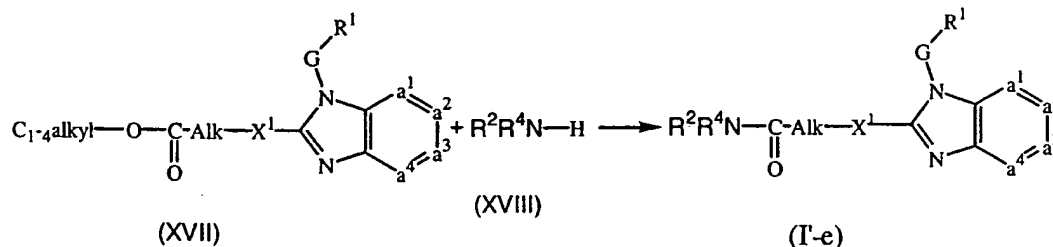
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and $R^{1a}-(A-O-H)_w$, $R^{1a'}-(A-O-H)_2$ and $R^{1a''}-(A-O-H)_3$ being defined as R^1 according to claim 2 provided that R^1 is substituted with hydroxy, hydroxy C_{1-6} alkyl, or $HO(-CH_2-CH_2-O)_n-$, with w being an integer from 1 to 4 and P or P_1 being a suitable protecting group, with a suitable acid.

5

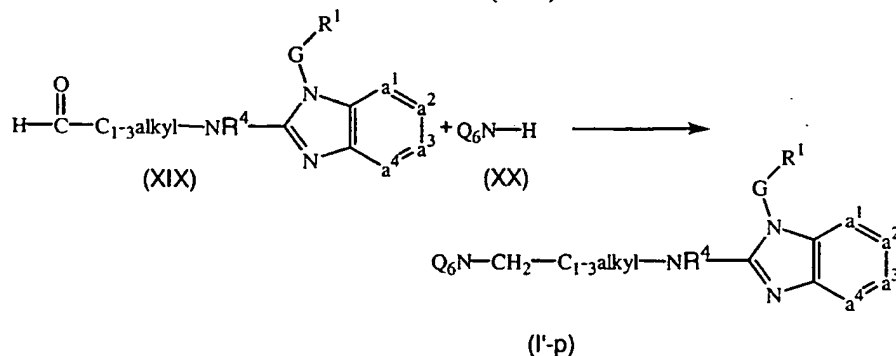
o) amination of an intermediate of formula (XVII)



with R^1 , G , $-a^1=a^2-a^3=a^4-$, Alk , X^1 , R^2 and R^4 defined as in claim 2, in the presence of a suitable amination agent;

10

p) amination of an intermediate of formula (XIX)



with R^1 , G , and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $Q_6N-CH_2-C_{1-3}$ alkyl- NR^4 being defined as Q according to claim 2 provided that in the definition of Q , X^2 is C_{2-4} alkyl- NR^4 , in the presence of a suitable amination agent;

15

and, if desired, converting compounds of formula (I') into each other following art-known transformations, and further, if desired, converting the compounds of formula (I'), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, metal complexes, quaternary amines or N -oxide forms thereof.

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16. A product containing (a) a compound as defined in claim 2 or 9, and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in the treatment or the prevention of viral infections.
- 5 17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) a compound as defined in claim 2 or 9, and (b) another antiviral compound.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/05676

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/06 C07D471/04 C07D401/14 C07D413/14 C07D417/14
 C07D405/14 A61K31/501 A61K31/4439 A61K31/454 A61K31/4184
 A61K31/4188 A61P31/14 //(C07D471/04, 235:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 099 139 A (JANSSEN PHARMACEUTICA NV) 25 January 1984 (1984-01-25) cited in the application claims ---	1-17
Y	EP 0 144 101 A (JANSSEN PHARMACEUTICA NV) 12 June 1985 (1985-06-12) cited in the application claims ---	1-17
Y	EP 0 145 037 A (JANSSEN PHARMACEUTICA NV) 19 June 1985 (1985-06-19) cited in the application claims ---	1-17

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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 September 2000

Date of mailing of the international search report

13/10/2000

Name and mailing address of the ISA

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Allard, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/05676

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 151 824 A (JANSSEN PHARMACEUTICA NV) 21 August 1985 (1985-08-21) cited in the application claims ---	1-17
Y	EP 0 151 826 A (JANSSEN PHARMACEUTICA NV) 21 August 1985 (1985-08-21) cited in the application claims ---	1-17
Y	EP 0 232 937 A (JANSSEN PHARMACEUTICA NV) 19 August 1987 (1987-08-19) cited in the application claims ---	1-17
Y	EP 0 295 742 A (JANSSEN PHARMACEUTICA NV) 21 December 1988 (1988-12-21) cited in the application claims ---	1-17
Y	EP 0 297 661 A (JANSSEN PHARMACEUTICA NV) 4 January 1989 (1989-01-04) cited in the application claims ---	1-17
Y	EP 0 307 014 A (JANSSEN PHARMACEUTICA NV) 15 March 1989 (1989-03-15) cited in the application claims ---	1-17
Y	EP 0 393 738 A (JANSSEN PHARMACEUTICA NV) 24 October 1990 (1990-10-24) claims ---	1-17
Y	EP 0 005 318 A (JANSSEN PHARMACEUTICA NV) 14 November 1979 (1979-11-14) cited in the application claims ---	1-17
Y	WO 92 01697 A (JANSSEN PHARMACEUTICA NV) 6 February 1992 (1992-02-06) cited in the application claims ---	1-17
Y	WO 92 01687 A (JANSSEN PHARMACEUTICA NV) 6 February 1992 (1992-02-06) cited in the application claims ---	1-17
Y	WO 98 10764 A (UCB, S.A.) 19 March 1998 (1998-03-19) claims ---	1-17

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/05676

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 058 146 A (UCB, S.A.) 18 August 1982 (1982-08-18) claims	1-17
A	--- R.R. TIDWELL ET AL: "Aromatic amidines : comparison of their ability to block respiratory syncytial virus induced cell fusion and to inhibit plasmin, urokinase, thrombin, and trypsin" JOURNAL OF MEDICINAL CHEMISTRY., vol. 26, no. 2, 1983, pages 294-298, XP002123605 ISSN: 0022-2623 the whole document	1
A	--- CHIBA T ET AL: "Inhibitory effect of pyridobenzazoles on virus replication in vitro" BIOLOGICAL & PHARMACEUTICAL BULLETIN, vol. 18, no. 8, August 1995 (1995-08), pages 1081-3, XP002148491 the whole document -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/05676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0099139 A	25-01-1984	US 4556660 A	03-12-1985
		AT 25459 T	15-02-1987
		AU 563363 B	09-07-1987
		AU 1672883 A	17-01-1985
		BG 40655 A	15-01-1987
		CA 1266267 A	27-02-1990
		DE 3369784 D	19-03-1987
		DK 318583 A	13-01-1984
		ES 524029 D	16-11-1985
		ES 8602768 A	16-03-1986
		FI 832521 A,B,	13-01-1984
		GR 81366 A	11-12-1984
		HU 203550 B	28-08-1991
		IE 56077 B	10-04-1991
		IL 69198 A	30-01-1987
		IN 156065 A	04-05-1985
		JP 59021680 A	03-02-1984
		KR 8701510 B	20-08-1987
		NO 832524 A,B,	13-01-1984
		NZ 204759 A	13-12-1985
		PH 22009 A	02-05-1988
		PL 242970 A	13-08-1985
		PT 77012 A,B	01-08-1983
		RO 87533 A	31-10-1985
		SU 1297728 A	15-03-1987
		US 4820822 A	11-04-1989
		US RE33833 E	25-02-1992
		ZA 8305044 A	27-02-1985
		ZW 15583 A	30-01-1983
		US 4760074 A	26-07-1988
EP 0144101 A	12-06-1985	AT 60769 T	15-02-1991
		AU 579121 B	17-11-1988
		AU 3602884 A	06-06-1985
		BG 43188 A	15-04-1988
		CA 1257258 A	11-07-1989
		CA 1330081 A	07-06-1994
		CZ 8409128 A	17-01-1996
		DE 3484096 D	14-03-1991
		DK 567884 A	31-05-1985
		FI 844708 A,B,	31-05-1985
		FI 884037 A,B,	01-09-1988
		GR 81097 A	04-04-1985
		HU 35677 A	29-07-1985
		HU 199837 B	28-03-1990
		IL 73686 A	31-05-1988
		JP 6092389 B	16-11-1994
		JP 60149583 A	07-08-1985
		KR 8800044 B	20-02-1988
		KR 8800489 B	08-04-1988
		KR 8800785 B	09-05-1988
		NO 844755 A,B,	31-05-1985
		NZ 210339 A	29-05-1987
		PH 23692 A	27-09-1989
		PH 26643 A	04-09-1992
		PL 250633 A	17-12-1985
		PT 79562 A,B	01-12-1984
		RO 90414 A	10-12-1986

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/05676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0144101 A		SK 912884 A	07-05-1997
		SU 1500162 A	07-08-1989
		SU 1694064 A	23-11-1991
		US 4888426 A	19-12-1989
		US 5025014 A	18-06-1991
		US 4695569 A	22-09-1987
		US 5126339 A	30-06-1992
		ZA 8409331 A	30-07-1986
EP 0145037 A	19-06-1985	ZW 19484 A	07-05-1986
		US 4634704 A	06-01-1987
		AT 40130 T	15-02-1989
		AU 565884 B	01-10-1987
		AU 3387284 A	18-04-1985
		BG 43007 A	15-03-1988
		CA 1247614 A	27-12-1988
		DE 3476204 D	23-02-1989
		DK 478484 A,B,	07-04-1985
		ES 536590 D	16-11-1985
		ES 8602763 A	16-03-1986
		FI 843934 A,B,	07-04-1985
		GR 80010 A	15-11-1984
		HU 38629 A,B	30-06-1986
		IL 73118 A	31-03-1988
		JP 7098818 B	25-10-1995
		JP 61010577 A	18-01-1986
		KR 8701509 B	20-08-1987
		KR 8701647 B	18-09-1987
		NO 844009 A,B,	09-04-1985
		NZ 209642 A	30-04-1987
		PH 21310 A	28-09-1987
		PL 249916 A	05-11-1985
		PT 79307 A,B	01-11-1984
		RO 90457 A	10-12-1986
		SU 1440346 A	23-11-1988
		ZA 8407847 A	28-05-1986
		ZM 4584 A	28-05-1986
		ZW 16484 A	30-04-1986
		IE 57722 B	24-03-1993
EP 0151824 A	21-08-1985	US 4588722 A	13-05-1986
		AT 51621 T	15-04-1990
		AU 575612 B	04-08-1988
		AU 3736385 A	01-08-1985
		BG 47033 A	16-04-1990
		CA 1246070 A	06-12-1988
		DE 3481841 D	10-05-1990
		DK 8885 A	10-07-1985
		ES 539266 D	16-01-1986
		ES 8604203 A	01-06-1986
		FI 850078 A,B,	10-07-1985
		GR 850059 A	11-01-1985
		HU 37780 A,B	28-02-1986
		IE 57968 B	03-06-1993
		IL 74017 A	31-03-1988
		JP 60174778 A	09-09-1985
		KR 8701046 B	26-05-1987
		NO 850084 A	10-07-1985

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/05676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0151824 A		NO 892563 A	10-07-1985
		NZ 210675 A	29-05-1987
		PH 21554 A	11-12-1987
		PL 251476 A	17-12-1985
		PT 79808 A, B	01-02-1985
		RO 91075 A	27-02-1987
		SU 1400509 A	30-05-1988
		ZA 8500186 A	27-08-1986
		ZM 385 A	29-08-1986
		ZW 585 A	30-07-1986
EP 0151826 A	21-08-1985	AT 87626 T	15-04-1993
		AU 573673 B	16-06-1988
		AU 3736485 A	12-09-1985
		BG 40965 A	14-03-1987
		CA 1259609 A	19-09-1989
		CZ 8500164 A	15-12-1993
		DE 3486121 A	06-05-1993
		DE 3486121 T	15-07-1993
		DK 8985 A	10-07-1985
		ES 539281 D	16-06-1987
		ES 8706668 A	16-09-1987
		FI 850079 A, B,	10-07-1985
		GR 850060 A	05-04-1985
		HU 36471 A, B	30-09-1985
		IE 59707 B	23-03-1994
		IL 74018 A	31-08-1988
		JP 7068240 B	26-07-1995
		JP 60185777 A	21-09-1985
		KR 8701169 B	15-06-1987
		KR 8800247 B	15-03-1988
		KR 9001545 B	12-03-1990
		KR 9001546 B	12-03-1990
		NO 850085 A, B,	10-07-1985
		NZ 210776 A	30-03-1988
		PH 23995 A	09-02-1990
		PL 251488 A	12-01-1987
		PT 79809 A, B	01-02-1985
		RO 90622 A	10-12-1986
		SU 1396964 A	15-05-1988
		US 4839374 A	13-06-1989
		ZA 8500187 A	27-08-1986
		ZM 285 A	29-08-1986
		ZW 485 A	30-07-1986
		US 4695575 A	22-09-1987
EP 0232937 A	19-08-1987	AT 79620 T	15-09-1992
		AU 583706 B	04-05-1989
		AU 6821887 A	06-08-1987
		CA 1327579 A	08-03-1994
		CN 87100563 A, B	19-08-1987
		CS 9103825 A	13-05-1992
		CY 1865 A	05-04-1996
		DE 3781173 A	24-09-1992
		DE 3781173 T	17-12-1992
		DK 54187 A	04-08-1987
		EG 17993 A	30-08-1991
		ES 2052544 T	16-07-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/05676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0232937 A		FI 870448 A	04-08-1987
		GR 3006158 T	21-06-1993
		HK 114695 A	21-07-1995
		HU 44544 A,B	28-03-1988
		IE 60885 B	24-08-1994
		IL 81448 A	17-09-1990
		JP 2063263 C	24-06-1996
		JP 7094393 B	11-10-1995
		JP 62215575 A	22-09-1987
		JP 7179458 A	18-07-1995
		JP 8019126 B	28-02-1996
		NO 870407 A	04-08-1987
		NZ 219165 A	26-04-1990
		PH 24738 A	01-10-1990
		PT 84234 A,B	01-03-1987
		US 4835161 A	30-05-1989
		ZA 8700744 A	26-10-1988
		ZM 1287 A	29-08-1988
		ZW 2087 A	31-08-1988
EP 0295742 A	21-12-1988	AT 79878 T	15-09-1992
		AU 600144 B	02-08-1990
		AU 1810988 A	22-12-1988
		CA 1324133 A	09-11-1993
		CN 88103784 A,B	28-12-1988
		DE 3874013 A	01-10-1992
		DE 3874013 T	07-01-1993
		DK 333288 A	20-12-1988
		ES 2045083 T	16-01-1994
		FI 882909 A,B,	20-12-1988
		GR 3006205 T	21-06-1993
		HU 48628 A,B	28-06-1989
		IE 61728 B	30-11-1994
		IL 86788 A	18-08-1992
		JP 1025776 A	27-01-1989
		JP 2609464 B	14-05-1997
		KR 9701158 B	29-01-1997
		NO 882641 A,B,	20-12-1988
		NZ 224928 A	26-04-1990
		PH 25532 A	24-07-1991
		PT 87742 A,B	01-07-1988
		SU 1644717 A	23-04-1991
		US 4897401 A	30-01-1990
		US 5006527 A	09-04-1991
		ZA 8804346 A	28-02-1990
EP 0297661 A	04-01-1989	AT 80628 T	15-10-1992
		AU 603684 B	22-11-1990
		AU 1835388 A	05-01-1989
		CA 1317939 A	18-05-1993
		DE 3874626 A	22-10-1992
		DE 3874626 T	25-02-1993
		ES 2052686 T	16-07-1994
		GR 3005715 T	07-06-1993
		IE 61360 B	02-11-1994
		IL 86921 A	15-11-1992
		JP 1034979 A	06-02-1989
		NZ 225080 A	26-02-1990

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/05676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0297661 A		PT 87866 A,B	30-06-1989
		US 4988689 A	29-01-1991
		US 5071846 A	10-12-1991
		US 5151424 A	29-09-1992
		ZA 8804696 A	28-03-1990
EP 0307014 A	15-03-1989	AT 83147 T	15-12-1992
		AU 608336 B	28-03-1991
		AU 1885388 A	12-01-1989
		CA 1324131 A	09-11-1993
		CN 1030587 A,B	25-01-1989
		DE 3876551 A	21-01-1993
		DE 3876551 T	15-04-1993
		DK 382388 A	11-01-1989
		ES 2042711 T	16-12-1993
		FI 883282 A,B,	11-01-1989
		GR 3006971 T	30-06-1993
		HU 47573 A,B	28-03-1989
		IE 61354 B	02-11-1994
		IL 87018 A	21-02-1993
		JP 1031782 A	02-02-1989
		NO 883069 A,B,	11-01-1989
		NZ 225151 A	26-04-1990
		PT 87939 A,B	30-06-1989
		US 4946843 A	07-08-1990
		US 5011842 A	30-04-1991
		US 5086056 A	04-02-1992
		ZA 8804946 A	28-03-1990
EP 393738 A	24-10-1990	AT 114653 T	15-12-1994
		AU 615612 B	03-10-1991
		AU 5295190 A	11-10-1990
		CA 2013892 A	07-10-1990
		CN 1046161 A,B	17-10-1990
		DE 69014385 D	12-01-1995
		DE 69014385 T	20-04-1995
		DK 393738 T	16-01-1995
		ES 2067645 T	01-04-1995
		FI 95702 B	30-11-1995
		GR 3015154 T	31-05-1995
		HU 58324 A	28-02-1992
		IE 65460 B	01-11-1995
		IL 94008 A	18-02-1997
		JP 2290874 A	30-11-1990
		NO 174851 B	11-04-1994
		NZ 233088 A	25-10-1991
		PT 93671 A,B	20-11-1990
		RU 2030415 C	10-03-1995
		US 5272150 A	21-12-1993
		ZA 9002664 A	24-12-1991
EP 5318 A	14-11-1979	US 4219559 A	26-08-1980
		AT 373887 B	27-02-1984
		AT 242579 A	15-07-1983
		AU 523352 B	22-07-1982
		AU 4529679 A	18-10-1979
		BG 38164 A	15-10-1985
		CA 1140119 A	25-01-1983

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/05676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 5318 A		CS 7902227 A	12-03-1987
		CY 1250 A	31-08-1984
		DE 2961740 D	25-02-1982
		DK 83183 A	24-02-1983
		DK 129879 A	04-10-1979
		EG 13913 A	30-09-1982
		ES 479206 A	16-12-1979
		FI 791084 A,B,	04-10-1979
		GR 64907 A	07-06-1980
		HK 3184 A	20-01-1984
		HU 182965 B	28-03-1984
		IE 47818 B	27-06-1984
		IL 56992 A	31-03-1983
		JP 1001477 B	11-01-1989
		JP 1523384 C	12-10-1989
		JP 54151982 A	29-11-1979
		JP 1117880 A	10-05-1989
		JP 1622522 C	25-10-1991
		JP 2040666 B	12-09-1990
		LV 5016 A	10-06-1993
		MY 4685 A	31-12-1985
		NO 791097 A,B,	04-10-1979
		NO 842563 A,B,	04-10-1979
		NZ 189978 A	31-05-1984
		PH 15877 A	13-04-1983
		PL 214648 A	24-03-1980
		PT 69429 A	01-05-1979
		RO 79320 A	17-08-1982
		SG 29883 G	19-04-1984
		SU 1056902 A	23-11-1983
		YU 50283 A	31-12-1983
		YU 78479 A	31-10-1983
		ZA 7901557 A	26-11-1980
		AT 373888 B	27-02-1984
		AT 453882 A	15-07-1983
		CS 8403451 A	12-03-1987
		KR 8300677 A	28-03-1983
WO 9201697 A	06-02-1992	AT 188477 T	15-01-2000
		AU 646280 B	17-02-1994
		AU 8209391 A	18-02-1992
		CA 2086546 A	20-01-1992
		CN 1058216 A,B	29-01-1992
		CS 9102239 A	19-02-1992
		DE 69131895 D	10-02-2000
		DE 69131895 T	20-07-2000
		EP 0539420 A	05-05-1993
		ES 2142802 T	01-05-2000
		FI 930199 A	18-01-1993
		HU 64066 A	29-11-1993
		IL 98865 A	27-11-1995
		KR 206723 B	01-07-1999
		MX 9100307 A	28-02-1992
		NO 304791 B	15-02-1999
		NZ 238863 A	26-03-1993
		PL 170580 B	31-01-1997
		PT 98366 A,B	29-05-1992
		RU 2067978 C	20-10-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/05676

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9201697	A		US 5360807 A	01-11-1994
			ZA 9105654 A	31-03-1993
WO 9201687	A	06-02-1992	AP 267 A	16-06-1993
			AT 171449 T	15-10-1998
			AU 644202 B	02-12-1993
			AU 8214191 A	18-02-1992
			BG 61342 B	30-06-1997
			BG 97314 A	18-01-1994
			CA 2086545 A	20-01-1992
			CN 1058215 A,B	29-01-1992
			CS 9102240 A	19-02-1992
			DE 69130255 D	29-10-1998
			DE 69130255 T	08-04-1999
			EP 0539421 A	05-05-1993
			ES 2121784 T	16-12-1998
			FI 930198 A	18-01-1993
			HR 930484 A	30-04-1996
			HU 64340 A	28-12-1993
			IL 98864 A	08-12-1995
			JP 3070951 B	31-07-2000
			KR 190299 B	01-06-1999
			MX 9100312 A	28-02-1992
			NO 300459 B	02-06-1997
			NZ 238864 A	26-08-1993
			PL 169361 B	31-07-1996
			PT 98365 A,B	29-05-1992
			RO 111768 A	30-01-1997
			RU 2059636 C	10-05-1996
			SI 9111263 A	30-04-1995
			SK 278133 B	07-02-1996
			US 5278165 A	11-01-1994
			US 5217980 A	08-06-1993
			ZA 9105653 A	31-03-1993
WO 9810764	A	19-03-1998	AU 717354 B	23-03-2000
			AU 4621397 A	02-04-1998
			BR 9712033 A	18-01-2000
			CN 1230116 A	29-09-1999
			CZ 9900830 A	16-06-1999
			EP 0936909 A	25-08-1999
			NO 991164 A	10-03-1999
			PL 332316 A	30-08-1999
			ZA 9707874 A	02-03-1999
EP 58146	A	18-08-1982	AT 8140 T	15-07-1984
			AU 544066 B	16-05-1985
			AU 8023182 A	12-08-1982
			BA 97198 B	02-08-1999
			BA 97199 B	02-08-1999
			CA 1199918 A	28-01-1986
			CY 1307 A	06-12-1985
			DE 3260282 D	02-08-1984
			DK 5388 A,B,	07-01-1988
			DK 44082 A,B,	07-08-1982
			ES 509358 D	01-08-1983
			ES 8307776 A	01-11-1983
			ES 521548 D	01-08-1984

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/05676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 58146 A		ES 8406455 A	01-11-1984
		FI 820318 A,B,	07-08-1982
		GR 75407 A	13-07-1984
		HK 86485 A	15-11-1985
		JP 1463099 C	28-10-1988
		JP 57149282 A	14-09-1982
		JP 63011353 B	14-03-1988
		LT 2553 R	28-02-1994
		LV 5494 A	10-03-1994
		MY 27987 A	31-12-1987
		NO 820297 A,B,	09-08-1982
		NZ 199650 A	06-07-1984
		PL 234935 A	09-05-1983
		PL 239687 A	18-07-1983
		PT 74390 A,B	01-03-1982
		SU 1227113 A	23-04-1986
		SU 1310397 A	15-05-1987
		SU 1287749 A	30-01-1987
		US 4525358 A	25-06-1985
		YU 23782 A	30-06-1985
		YU 223584 A	30-06-1985
		ZA 8200752 A	29-12-1982
		HU 184989 B	28-11-1984